U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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PUBLIC MEETING ON OVERSIGHT OF
LABORATORY DEVELOPED TESTS

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TUESDAY, JULY 20, 2010

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The meeting came to order at 8:00 a.m. in the Auditorium of the Marriott Inn and Conference Center, University of Maryland University College, 3501 University Boulevard East, Hyattsville, Maryland, Alberto Gutierrez presiding.

PRESENT:
ALBERTO GUTIERREZ, PhD, Director, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH
JEFFREY SHUREN, MD, JD, Director, Center for Devices & Radiological Health, FDA
MARIA CHAN, PhD, Director, Division of Immunology & Hematology Devices, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH
COURTNEY HARPER, PhD, Director, Division of Chemistry & Toxicology Devices, CDRH
SALLY HOJVAT, PhD, Director, Division of Microbiology Devices, Office of In Vitro Diagnostic Device Evaluation & Safety, CDRH
KATHERINE SERRANO, Office of In Vitro Diagnostic Device Evaluation & Safety, CDRH
LEONARD WILSON, Office of the Center Director, CBER

ALSO PRESENT:

PUBLIC PRESENTATIONS SESSION 2:

PATRICK TERRY, European Personalized Medicine Coalition
VICTORIA PRATT, PhD, Quest Diagnostics, Nichols Institute
DAVID MONGILLO, American Clinical Laboratory Association
MICHAEL MURPHY, MSc, Conatus Consulting, LLC
ELAINE LYON, PhD, Association for Molecular Pathology
ANGELA CALIENDO, MD, PhD, President, Pan-American Society for Clinical Virology
MITCH NELLES, PhD, XDx
ANNA LONGWELL, Longwell & Associates
KATHY HIBBS, Genomic Health
WILLIAM CLARKE, PhD, American Assoc. for Clinical Chemistry
LIZ LISON, Advocea, LLC
KLAUS SCHAFER, MD, TessArae, LLC
FRANK COCKERILL, MD, Mayo Clinic
PAULA REVELL, PhD, American Society for Microbiology
PHOEBE MOUNTS, Morgan Lewis
MICHAEL P. RYAN, PhD, Wadsworth Center New York State Department of Health
ELISSA PASSIMENT, American Society for Clinical Laboratory Science
BRUCE DAVID, MD, Clinical Cytometry Society, International Council for Standardization in Haematology & Trillium Diagnostics
GAIL VANCE, MD, FCAP, College of American Pathologists (CAP)
RICHARD NAPLES, Becton Dickinson & Co.
SHASHIKAN KULKARNI, PhD, Washington University School of Medicine
TED SNELGROVE, Crescendo Bioscience
KATHLEEN RAO, PhD, American College of Medical Genetics
ANDREA ZACHARY, PhD, American Society of Histocompatibility & Immunogenetics

GEORGIRENE VLADUTIU, PhD, Kaleida Health Laboratories & SUNYAB & Pres., Society

for Inherited Metabolic Disorders
JUDITH YOST, MA, MT (ASCP), Centers for Medicare & Medicaid Services
JOHN E. TOMASZEWSKI, MD, American Society for Clinical Pathology
JOANNE BARTKUS, PhD, Minnesota Public Health Laboratory
BERNARD SIXT, PhD, Agendia
SALVATORE SALAMONE, PhD, Saladax Biomedical
MARY DEL BRADY, CvergenX, Inc.
GUALBERTO RUANO, MD, PhD, Hartford Hospital
ROBERT MIDDLEBERG, PhD, NMS Labs

SESSION 2 DISCUSSION:

THOMAS HEARN, PhD, Center for Disease Control & Prevention, Session Moderator
KAREN P. MANN, MD, PhD, Association for Molecular Pathology
ALAN MERTZ, American Clinical Laboratory Association
RICHARD NAPLES, Becton Dickinson & Co., AdvaMed
TIMOTHY O'LEARY, MD, PhD, Veterans Health Administration
GAIL VANCE, MD, FCAP, College of American Pathologists
JUDY YOST, MA, MT (ASCP), Division of Laboratory Services, Centers for Medicare & Medicaid Services

PUBLIC PRESENTATIONS SESSION 3:

ANNE WOJCICKI, 23andMe, Inc.
ADELE SCHNEIDER, MD, Albert Einstein Medical Center
JEREMY GRUBER, Council for Responsible Genetics
KATHERINE BORGES, International Society of Genetic Genealogy
DESTRY SULKES, MD, Medivo, Inc.
DAVID BECKER, PhD, Pathway Genomics
AMY DuROSS, Navigenics
KENNETH EMANCIPATOR, MD, American Society

C-O-N-T-E-N-T-S

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

8:00 a.m.

DR. GUTIERREZ: Good morning. Can everybody, please, take their seats and we will start? So before we start the session, I wanted to deal with just two issues. We wanted to clarify, there were a couple of things said yesterday that we wanted to make sure were clarified.

And the first one has to do with the EUA process and what happened with pandemic flu. And I would like Dr. Hojvat to address that. Sally?

DR. HOJVAT: Yes. We had a really interesting year, as you can imagine. Just to give you an idea, I know someone was saying that the timing can be a problem with the FDA. Let me just tell you how we worked.

There was a five hour one, by the way, that Steve talked about, but that was H5 many years ago. But this one was pretty good, too.

We heard from the CDC on a Thursday that they were worried about a particular strain that, as everybody knows the story, had been picked up in California. And we worked with them over the weekend, literally we did, that part is true.

The emergency was declared on the Sunday, I

believe, April the 26th. We authorized the CDC assay on the 27th. So a day after the emergency was declared, the CDC was authorized to ship out to all of the public health labs and the LRN Labs their assay. So there was a one day lag, perhaps, in getting that out to the field.

During that year, we received 28 different applications for EUA. Now, what we were doing with the EUA was really basically looking at the analytical data. We weren't asking people to go out and do clinical studies as part of the emergency authorization that we assess and do a risk assessment on analytical data.

We published a template to make it easy for people. That went through very quickly for a guidance document. That was out so that people knew exactly what studies, and we outlined them, were to be done.

We had comments from people, for example, the Molecular Group, AMA, they said that our validation was what they thought was an ideal validation for a lab-developed test. So we were asking no more, no less than the experts in the field feel is necessary to be able to validate the performance, analytical performance of the test.

Given that, we had, as I said, 28 different

applications, 16 different amendments to those applications, as people began to ask for more specimen types, different specimen types, because it appeared that we needed to expand that, the types of specimens coming into the public health labs and other labs was much greater than we had originally authorized.

Of those 28, we actually authorized 19, 19 different tests, for 2009 H1N1. What we tried to do, and some of it was beyond our ability to do, was try and make sure that we were covering a big large expanse of the population at the laboratories.

We contacted companies who had instruments that we knew were widely distributed and said, you know, we would really like you to have an assay that could go on your instrument, because your instrument is very widely distributed.

That didn't always work. Again, that was beyond our ability to persuade companies to submit an assay to us or if they did, it was very late in the game.

I said 19, that meant that about 10 did not go through the authorization process. Why didn't they? Some withdrew it when they just decided they didn't want to do that. Some decided they wanted to go on to do 510(k)s which is, of course, what we are trying to do now to get ready for the next flu

season, and they went for what we call the PreIDE process, which you heard about yesterday.

And others, a couple of others, we said, your data is not supporting it. It wasn't supporting that very low minimum amount of analytical data.

Interestingly enough, two of those assays realized that when we had sent them back our responses, their assays, indeed, were not performing correctly and were actually missing. They did not have the right probes and they went back to redo their assays. So that was an interactive process.

Again, those were lab-developed tests where they said, yes, you have discovered that, in fact, our assays are not where they should be and they went back to redevelop their assays.

So, overall, we were able to cover -- those EUAs covered, not only the CDC, but the Department of Defense assays, commercial, IVD companies, reference laboratories, as well as quite a few smaller companies.

The smaller companies, you know, in a way were not exactly what was needed, but we went through the process to give them some idea of what they would need to do at least for a 510(k) where they could do it commercially.

So that's basically what happened. I think we did cover. We calculated the number of tests that were done by EUAs as being over 1.6 million by the end of the -- when they finally declared the emergency over June 26th, I believe.

So if there are any questions on that, maybe you can see me afterwards. I hope I clarified that we did react very quickly and responsibly towards the pandemic flu.

DR. GUTIERREZ: The second point I wanted to make was on CLIA and analytical validation. CLIA does -- when they do inspect or the certified bodies do inspect, they look to see that the laboratory-developed tests or DTC tests actually has the correct analytical validation.

But typically they do this on inspection, so they don't have time to really wade through the data. And it is not unusual for them when they do have questions to collect the data and then, for example, ask the FDA to help them look at the data.

It's just impossible to, on inspection when they are looking at everything else, also sit down and really go through carefully a bunch of analytical validation.

So with that, we're going to start this morning and we are going to try to go through fairly quickly, so that we can get you off early and those people who have planes can catch the

planes.

MS. SERRANO: Hi, I just wanted to remind speakers that we do have a lot of people that are speaking today, so if they could please, just before they are going to speak, sort of be in this general area, so that the transition can be a little quick.

I'll be giving hand signals. I'm going to have to enforce the five minutes pretty strictly today, just because we do have so many people and we do want to get out of here on time. And so, please, you know, be respectful and don't make be bring out the big measures. I don't want to cut anyone off.

So actually, we're going to rearrange the schedule just slightly. Dr. Patrick Terry is going to be speaking first. And then we will start with Victoria Pratt after that.

MR. TERRY: Well, first, I would like to say thank you to the FDA, especially appreciation for Katie and how she has orchestrated this meeting and change of venue and handled these two days. I think it's fabulous.

So I would like to start off today with a collective "you're welcome" to the community of kind of precipitating changes in enforcement discretion on one of the co-founders of Genomic Health and trying to advance an industrialized approach to advanced diagnostics through the CLIA delivery model.

But I'm here today to talk about the European Personalized Medicine Coalition. I started the PMC here in the United States to organize a collective and diverse community to understand and manage personalized medicine and where advanced diagnostics will take public policy and reimbursement and so forth.

And now, we are working on the European platform. I have started a number of companies now, after leaving Genomic Health and some of them in Europe.

So the Personalized Medicine Coalition of Europe or EPEMED is founded recently and even though it's a European Union, we have a terrific amount of fragmentation. I'm not as cynical or pessimistic as Steve Gutman is about the enforcement and the CE pathway marking.

And while it is true that reimbursement is a technical difficulty in Europe and -- it's not quite, as described by Steve, a deliberate rationing approach. But there are significant differences with health technology review and reimbursement fragmentation decision making in Europe.

But speaking with health ministers and nation states over the last few months, the central points of decision making are quite clear, and the nervous system of decision making

at the Pan-European level has some significant advantages than the U.S. for platform opportunities and introduction of advanced diagnostics in Europe.

So our objectives are really to focus and be a hub for communication and it is certainly our hope that we can leapfrog some of the challenges that are presented by advanced diagnostics in work in a deliberative way to be adaptive and responsive of where the FDA is going and making sure we have some sense of alignment in Europe as well around all of these issues and how to develop and understand best practices and pursue novel validation approaches, so feasibility-wise, these diagnostics can be developed to meet evidentiary thresholds, but in a timely manner.

The Steering Committee is a diverse set of a number of companies. The membership is expanding rapidly, a similar growth pattern that took place in the PMC here in the United States.

But quickly to jump to the questions, you know, there are a number of issues that we are interested in understanding what it really is this role of the Diagnostic Test Registry the NIH has announced. We are a little disturbed that it is not mandatory, so there is questions there about its actual utility

and adherence.

There is concern, certainly from European developers, there is concern about EU-only data in a submission package, whether that will be acceptable or not. While the Agency may understand some of these issues and have a clear thought pattern, it's not well-understood in the community.

We are struggling also with some novel statistical methodology that can be used with full genomes and other activities and adaptive clinical trials and Bayesian mathematics and primary and secondary endpoints and diagnostic trials that are not traditional, as well as this challenge of truly understanding and defining what fit for purpose means in archival studies.

And really if we could have guidance or some robust pathway analysis of really what is best practices to capture and understand all of the variables associated or biases with collections in retrospect of studies that would certainly be helpful to streamline the process of submission and protocol design in archival tissues.

And our final statement is certainly that we want to be a contributor to this process. We want to engage the FDA and have an opportunity to exchange. We will certainly submit comments to the docket.

But not unlike here in the United States, personalized medicine or advanced diagnostics falls into this gap between bio and pharma and ACLA and the 21st Century Medicine Coalition and the PMC have surrounded this issue from a variety of organizational standpoints, we don't have that same similar fragmentation in Europe, so we are hoping to have a unified voice around some of these issues.

And while the regulatory hurdles may increase in the United States, they are probably actually going down in Europe. So we will have to manage that effectively. So thank you for your attention.

(Applause.)

MS. SERRANO: Our next speaker this morning will be Victoria Pratt.

DR. PRATT: Hi. My name is Dr. Victoria Pratt. I'm Chief Director of Molecular Genetics at Quest Diagnostics. In addition to my responsibilities at Quest Diagnostics in validating new LDTs, I have also served on several advisory committees, including SACGHS oversight of genetic testing, the CDC's MMWR, CLSI and EurogenTest Work Group for Analytical Validation.

Quest Diagnostics is the world's leading provider of diagnostic testing, information and services that patients and

doctors need to make better health care decisions.

The company offers a broad menu of testing through a national network of laboratories, patients, service centers. All right. Now, you've got me nervous. Okay. And we serve over 150 million patients annually.

On behalf of Question Diagnostics, I'm here today to present our views on the FDA oversight of LDTs.

We in the laboratory industry are committed to quality of testing and patient health care. As scientists and laboratory professionals, we share the objectives of improving the quality of laboratory testing and improving health care.

While the FDA shares these same objectives, we raise the concern that simply extending FDA oversight from IVDs to LDTs will lead to potentially adverse unanticipated consequences.

Based on our substantial experience with LDTs, I share some of our concerns with the broad oversight concept:

1. Will the broad potential value of additional oversight outweigh the burden and costs? Clinical laboratories are currently regulated by CLIA and multiple state agencies. In addition, we may be also regulated by New York State and CAP.

As stated yesterday, New York State currently conducts a pre-market review of all LDTs focusing on analytical

validity and clinical validity through the use of clinical evidence.

The New York State process can take over a year and will the additional FDA oversight add sufficient value to that? As a first step, we propose avoiding delay. We propose grandfathering current LDTs that are approved by New York State.

2. Will additional oversight interfere with continuous improvement of testing and slow innovation? The FDA has a QSR Program for diagnostic products created and sold by manufacturers to any laboratory that will follow the package insert.

Similarly, when a laboratory creates a test solely used within that laboratory, we ensure the quality by validating the assay before it can be offered and to assure post-market quality by adherence to the laboratory's quality assurance, quality control and quality management systems, which must meet guidelines set forth by CLIA and CAP and state agencies.

In addition, we also voluntarily complied to CLSI and ISO15189. Test validation is not a onetime event, I can't say that enough, but rather, a continuous process where we are constantly improving and cross-validating our assays.

It is those very improvements that, under the FDA oversight, may create a regulatory burden on FDA reviewers and

potentially retarding adoption of more innovative techniques on existing tests.

3. Will the FDA be properly resourced to efficiently review a large number of LDTs from thousands of laboratories? LDTs are performed in many settings, from large reference laboratories to small single-source laboratories.

Unlike pre-market review of IVD products, where there is a single application, the FDA would have to conduct pre-market review for every lab's LDT given for a condition or a disease. It's an enormous, unprecedented increase in workload on the FDA.

Yet if the FDA took the approach of only focusing on a few tests, their laboratories would still have to follow or comply with an entirely new regime, QSR, design controls, FDA inspections, simply because a few tests are a real concern of the FDA.

Instead, we propose that we identify material gaps in quality of the laboratory services at most risk and design and adopt improvements in oversight and close those gaps.

4. Will pre-market review requirements prevent new tests for rare conditions or tests based on the latest scientific developments from becoming available? Within Quest

Diagnostics, we will offer a variety of LDTs, because there is no comparable assay available due to the rarity of the disease or condition, the FDA-cleared assay does not meet our capacity requirements or the test does not reflect the latest scientific development.

The volume of many of these tests may not support a new broad-based regulatory approach.

5. Lastly, will pre-market review requirements preclude laboratory cooperation that leads to better and more standardized tests for the same condition? Many laboratories perform the same or very similar assays, as there are no FDA-cleared assays for most molecular genetic testing and oncology disorders.

Over time, we have standardized the process of these tests. And I would like to highlight, one is the CDC's GeT-RM Project where we verify reference materials for all laboratories for the same.

Patients are the center of everything we do and I thank you for your time and attention.

(Applause.)

MS. SERRANO: Our next speaker is David Mongillo.

MR. MONGILLO: I'm David Mongillo, Vice President for Policy and Medical Affairs at the American Clinical Laboratory Association.

ACLA represents clinical laboratories throughout the country, including local, regional and national laboratories. All ACLA members produce and perform LDTs and thus will be directly affected by change in the oversight of these tests.

It is important to emphasize the breadth, scope and value of all lab services that could be considered an LDT. This will demonstrate the need to move the oversight of LDTs forward in a measured way that does not have unintended consequences for patient care.

Independent and hospital-based clinical laboratories, physician pathology practices and university medical centers all develop and validate tests in their own laboratories for physician-directed patient care.

Examples of low risk, well-understood LDTs can include Pap smears, manual blood cell counts, erythrocyte sedimentation rates, microbiology cultures and sensitivity tests among many others.

These range to the new advanced diagnostics that derive from the mapping of the human genome and will help fulfill

the promise of personalized medicine.

In addition, when an FDA-cleared test is modified by the clinical laboratory to improve the test, it is considered to be a laboratory-developed test. Clinical laboratories continually seek ways to improve tests.

Resubmission to FDA for every change improvement will delay innovation and be a disincentive for assay improvement.

LDTs have proven value. They provide major health care breakthroughs, especially in cancer and infectious disease. Two examples of many advances for cancer therapy for which no current FDA-cleared assay exists are the generic test bcr/abl for monitoring the effectiveness of therapy for chronic myelogenous leukemia and K-ras, a therapeutic biomarker for metastatic colon cancer.

Infectious disease testing for herpes meningitis in spinal fluid and cytomegalovirus in immunocompromised individuals are two examples of infectious disease testing where an FDA-approved cleared test is not available.

Tests developed by clinical laboratories have also played a critical role in the nation's emergency preparedness by allowing for the timely identification of SARS, Avian Flu, West Nile

Virus and more recently H1N1.

Hopefully, LDTs will continue to be available to assist in the identification of new emerging pathogens.

All of these examples illustrate the importance of assuring a continued rapid accessibility to the latest science and the need for test oversight that evolves in a flexible and balanced way.

There are many more examples of LDTs in use that allow for rapid response to keep pace with our nation's most costly and menacing chronic diseases and emerging public health threats.

Moving forward, it is critically important for stakeholders and FDA to work together to identify oversight gaps and to prioritize actions according to risk. Although we thank FDA for this important two day meeting, the process should be a longer, more deliberative, open, transparent approach.

Some of the crucial steps on the path forward include: to identify and better understand the differences between laboratory services and commercial IVDs, to reach consensus on the gaps in the oversight of these laboratory services, discussion towards consensus of the criteria for risk-based categories of tests and the appropriate evidence requirements

based on those categories, recognition of the need to grandfather the vast majority of well-accepted and well-understood tests already in clinical use and discussion of the gaps between FDA quality systems regulations and CLIA.

We ask that FDA approach this discussion with an open agenda and a commitment to flexibility and balance.

Since clinical laboratories are not traditional medical device manufacturers, applying a strict paradigm based upon the regulation of traditional medical devices and applied to all LDTs will have a major consequence to clinical laboratories and will place those laboratories in jeopardy of being unable to comply and, in many cases, unable to continue the important work in the development of cutting-edge LDTs.

This will have unintended effects of slowing the availability of important tests and negatively affecting patient care.

ACLA members are the experts in how clinical laboratories operate, including how tests are developed, validated and how quality is ensured. We recognize the need to communicate that information more effectively to FDA.

We also recognize that we must better understand FDA's regulation of medical devices. We hope to continue a constructive two-way communication with FDA

towards this shared understanding and we pledge our active support and engagement to reach a timely and productive outcome. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is Diane Allingham-Hawkins. Dr. Hawkins? Okay. If she is not here, then I guess we will move to Dr. Michael Murphy.

MR. MURPHY: Good morning. I always like to start on a positive note and congratulate our industry and our regulatory agencies for no longer referring to the subject matter that we have been talking about for the last two days as home brews. So let's congratulate ourselves for calling it LDTs. It sounds so much more civilized, don't you think?

I'm Michael Murphy. I'm President of Conatus Consulting. I'm here representing our stakeholders, which include CLIA laboratories, help several companies setting up CLIA laboratories. I myself have set up 13 labs, six of which were CLIA labs in the past, also representing IVD manufacturers and third, pharmaceutical companies developing companion diagnostics.

So as I was getting ready for this talk and trying to figure out what I can say meaningfully in five minutes, I was going through the past history, including looking at presentations I have

given 20 years ago and meetings I have had with FDA like this one, and I just more and more started feeling like I was in the Bill Murray Groundhog Day movie. And so I wonder if a lot of us didn't.

And the reason I'm taking a few minutes to put this slide up there is to remind everybody we have been down this road before, so it might be helpful to look at what did we do right and why does this subject keep coming up? And what approach did the FDA take to make this a friendly transition, if that's what is going to happen?

So this hasn't come up even recently with Dr. Gutman testifying before Congress on the safety and quality of in vitro diagnostics back in 2006, but I was glad to see Dr. Harper's talk on history and realized that it wasn't just an aging process for myself that I was maybe dreaming we have been down this road before.

So what can I add in five minutes? So I'm going to cover five things very quickly, obviously.

One is, who is in charge? My suggestion or compromise for the industry and the FDA is to look closer at things that we already have in place like QSR for IVD FDA-cleared products. Talk about what is missing for these LDT so-called

building blocks. And then very quickly propose a model to ensure quality and reliability of LDTs going forward.

So this is not an insignificant problem. And so the reason I'm bringing this up is because when we propose the alphabet soup that we are confronted with in all three of the domains that I discussed in the beginning, that is CLIA, IVD and companion diagnostics, you know, we have these lab directors and medical directors who are overwhelmed and perplexed by the number of agencies that they have to already either on a voluntary basis or are forced through regulatory domains to apply to and to provide information to.

So you know, adding a couple more to this would just be making a significant problem worse. And at the same time, I don't see anybody else talk about this, but there is currently consultation period in the EU for very much the same subject.

And so I would also advise for our international clients that there be some harmonization here with regards to the process FDA is contemplating, what appears to be very similar things that are going on in Europe.

And this is just a reminder that we already have a good process if you are in the IVD world. These requirements are, in fact, the ones that we follow, as an IVD manufacturer, to make

sure we produce safe and effective products.

So what's really missing for LDT building blocks? That's a phrase that FDA uses in some guidance documents.

One is a use of cGMP manufacturing reagents. There was at least 10 or more companies that came about in the United States over the last decade who tried at least to offer these reagents. Without an endorsement, without a regulatory pathway for producing these products, LDT users are not incentivized to use GMP manufactured products.

So why do we have a directive from the FDA to follow an IVD 510(k) process for in vitro diagnostics and yet we let laboratories use either research grade reagents or general purpose reagents?

I am also recommending independent certification, not a government agency, not a laboratory association, but an independent third party, a not-for-profit group that people can submit their data to and get some kind of, in quotes, "certification."

And then a third recommendation is validation of combined laboratory-developed building blocks. That is, let the manufacturers, who are making these individual products like primers, probes, master mixes in the case of genetics, put them

together and test them and submit that data to the FDA. They have the data. And let people order out of catalog products that are known to work together, having been manufactured under GMP.

And fourth, QSR manufactured analyte specific reagents restricted by the FDA, despite a lack of intended use labeling and lack of regulatory and financial incentives to use GMP controls and reagents.

So just to finish, my recommendation is, require use only of GMP manufacturers, allow the labs to self-register, maybe look at the CE model, allow device manufacturers to disclose reliability and validation.

And last, I think the weakest link for the entire industry is the fact that we don't use GMP manufactured controls and standards. And if we don't fix this problem, all the work that we are doing here and that we do forward is going to be a waste, because this is the gold standard. Thank you.

(Applause.)

MS. SERRANO: The next speaker is Elaine Lyon.

DR. LYON: The Association for Molecular Pathology, AMP, commends the FDA for responding to our request for a public workshop. And we thank the organizers for the

opportunity to participate.

AMP believes that LDTs are an essential and central component of medical practice without which the practice of medicine that we know today would be severely reduced in scope. These tests continue to play formative roles in delivery of preventive care, diagnosis and disease management.

We have submitted our full comments to the docket and will summarize the key points now.

A regulatory model should not interfere with the practice of medicine. It is important to recognize how the current oversight system, which has included focused FDA oversight, enables clinical laboratories to rapidly incorporate new findings and to modify existing laboratory tests.

AMP strongly urges the FDA to preserve that flexibility with new or modified approaches to LDT oversight.

With that empiric data, it is difficult to assess the value of any oversight approach in protecting public safety. AMP encourages the FDA to collect data and assess the effectiveness of existing oversight models prior to implementing new approaches.

Any proposed oversight system must demonstrate that it would lead to improved health outcomes.

I'm sorry, I was one slide behind. Some LDTs

may need additional oversight. AMP believes that LDTs and all disciplines of laboratory medicine should be subject to the same oversight mechanisms and that molecular tests should not be singled out for heightened scrutiny.

AMP does agree that some tests may require additional regulatory review, including those that use a nontransparent algorithm with multiple markers that cannot be elucidated by other test developers or rely on a technology that is not easily replicated in multiple laboratories and for which a false result would cause significant morbidity or mortality or a false result could have widespread adverse effect for public health.

For these tests, the quality of the result is difficult to assess in an external review, such as an inspection, even for those knowledgeable in the field.

It is important to recognize that increased oversight of infrequently utilized tests could be overly burdensome and cost prohibitive. Acknowledging that all tests must meet the same high standards, there needs to be a mechanism to allow laboratories to continue providing these low-volume critical clinical services.

Any oversight protocol must address barriers to test development. AMP believes that the best approach to

achieve consistent and comparable quantitative data among laboratories is through the use of internationally established reference reagents.

Recently, AMP has been collaborating with NIST and CDC's GeT-RM Program to develop standard reference materials and validate existing publicly available human cell lines. The administration should support continued investment in these programs.

A major hurdle for the laboratories is securing coverage and reimbursement for tests they provide. Escalating costs for test development compounded with additional costs to satisfy new regulatory requirements could result in the elimination of important clinical tests.

In considering revisions to the current oversight processes, AMP urges FDA to realize the potential ramifications on test availability due to economic considerations.

And we have recommendations for a place to start. Developing validation standards could constitute a first step in ensuring the quality of performance of LDTs. Although minimum standards and guidances exist, there is room for improvement.

AMP is willing to participate with other

professional organizations to develop and promote such standards. As noted previously, AMP agrees that some tests may warrant additional regulatory review.

We recommend that FDA appoint an external advisory committee composed of individuals with relevant expertise to assist in identifying appropriate risk classifications.

As the FDA considers its approach to regulating LDTs, AMP encourages the Agency to consider the unanticipated effects that significant modifications to the current oversight system could represent for clinical laboratories, which in turn would adversely impact the delivery of effective care to our patients.

Thank you very much for considering AMP's comments in the LDT oversight. AMP looks forward to partnering with the FDA and continuing to work with the Agency for the benefit of patients. Thank you.

(Applause.)

MS. SERRANO: The next speaker will be Angela Caliendo. She is replacing Richard Hodinka.

DR. CALIENDO: Good morning. I'm Angie Caliendo and I'm representing the Pan- American Society for Clinical Virology. I'm going to provide a few background

comments and then some suggestions for the FDA to consider.

As many of you realize, molecular testing has revolutionized the practice of infectious diseases. And clinical virologists have been pioneers in the application of molecular techniques to clinical diagnostics.

We have been developing, validating and performing qualitative and quantitative testing for clinical use since the mid-1990s. The clinical utility of these tests has been very well-established. And the vast majority of LDTs in clinical use today are for infectious diseases.

LDTs for infectious diseases have primarily been developed out of necessity because of the significant void of commercialized FDA-cleared tests. Molecular testing is the standard of care for the detection and quantification of many pathogens for which there is no FDA-cleared or approved test available.

For example, central nervous system infections due to Herpes simplex virus and Varicella zoster virus and for monitoring CMV, BK virus, adenovirus and EBV in transplant recipients.

In short, laboratory-developed molecular tests are now essential for the practice of infectious diseases. LDTs for

infectious diseases are still primarily developed and used within individual institutions as part of the care and management of defined local patient populations.

Since testing is almost entirely on-site, substantial physician feedback about quality and impact of testing are readily available, thus allowing for continuous improvements of LDTs.

Clinical laboratories have never been under greater cost constraints than they are today. A regulatory process for LDTs that is overly burdensome and expensive will limit access to testing and negatively impact clinical care.

Large tertiary centers with critically ill, often immunocompromised, patients are highly dependent on LDTs.

With this as background, we respectfully provide the following suggestions:

The FDA should work with CLIA to bring consistency to the current regulatory process. This can be done in partnership with CLSI, the CDC and CAP. For example, the CAP checklist for molecular microbiology has been completely revised to include a section specific for LDTs.

By working with these organizations, it should be possible to establish practical guidelines for assay verification and validation that can be applied to all CLIA-certified laboratories

without the need for an additional regulatory process.

Clear and realistic guidelines for validation should be set for laboratories that modify FDA-cleared tests. The ability to use different extraction methods or an alternative, but comparable, real-time instrumentation is very important for laboratories, as purchasing a wide array of instruments and/or systems is not realistic or possible.

With the risk stratification approach proposed by the FDA, the impact of an incorrect result needs to be balanced with the consequences of not having the test available or potentially using inferior testing methods, such as viral culture or antigen detection or having results delayed such that they no longer impact clinical care.

When considering how to regulate LDTs, we suggest that the FDA carefully assess the resources needed for the process to avoid delays in approval, as this could limit access to testing. It may be helpful for the FDA to communicate with laboratory directors in New York State to obtain a perspective on the outcome of the extensive regulatory process that is required for LDTs and how the time for approval impacts access to testing.

We encourage the FDA to work with members of professional societies, such as those represented at this meeting in

establishing these guidelines. This represents a pool of highly knowledgeable and technically skilled individuals who can offer a real-world perspective.

We also encourage the FDA to work with international organizations to help establish standard materials and calibrators for molecular tests.

Finally, we ask the FDA to work with professional organizations to establish and fund a specimen repository that could be used by laboratories for test validations, with particular focus on rare pathogens or alternative specimen types.

For example, rectal or eye swabs for Chlamydia trachomatis. The repository could be used by commercial companies willing to submit a test to the FDA. Establishing and maintaining a repository would require resources for organization and oversight, but could assist in ensuring uniform quality of LDTs.

As we move forward with this process, it is essential that we are very mindful of unintended consequences. Actions that create a burdensome regulatory process, slow turnaround time, increased costs or limit access to testing will have a significantly negative impact on the quality of patient care.

On behalf of the Pan-American Society for Clinical Virology, I thank you for the opportunity to comment.

(Applause.)

MS. SERRANO: Our next speaker will be Mitch Nelles.

DR. NELLES: Good morning. I'm Mitch Nelles. I'm the Vice President of R&D and Technical Operations at XDx. It's worth mentioning XDx is a charter member of the Coalition for 21st Century Medicine and also a member of ACLA.

My talk today is from the perspective of one of a handful of companies who have already obtained FDA-clearance for the LDT.

In this brief presentation, I will be speaking about two issues, which are specific to AlloMap Molecular Expression Testing, which resulted from our decision to be an early adopter of the IVDMIA guidance.

First, a little bit of background about AlloMap. AlloMap is a 20 GNLDT based on the results from our Landmark CARGO Study. The test uses quantitative real-time PCR to measure the gene expression levels of 11 informative and 9 quality control normalization genes and employs an algorithm to convert the PCR results into a score from zero to 40.

AlloMap testing is performed only in the XDx Laboratory located in Brisbane, California. The lab was

CLIA-certified in November of 2004 and AlloMap was launched in early 2005. We have obtained numerous state agency certifications, including New York State, since that time.

Importantly and relevant to this meeting, in August of 2008, AlloMap was cleared by FDA as a Class II de novo 510(k) with the following indication for use: To aid in the identification of heart transplant recipients with stable allograph function who have a lot probability of moderate or severe acute cellular rejection at the time of testing in conjunction with standard clinical assessment. Poetry, isn't it?

Anyway, additional claims are under review by FDA following completion of our second landmark study, the IMAGE Study, which was designed to demonstrate AlloMap non-inferiority compared to biopsy for the clinical management of stable heart transplant patients. Results of the study were recently published in the New England Journal of Medicine.

I want to share two concerns and then associated proposed recommendations, which are related to being regulated by both CLIA and FDA.

It is well-known; obviously, at this meeting that CLIA and FDA utilize different quality systems for the inspection of IVD kit manufacturers and clinical labs. These quality systems are

overlapping and manageable in many cases, but are unique and potentially conflicting in some other instances.

For example, many LDTs are not distributed kits. LDT reagents and lab instruments are usually utilized by a single in-house reference laboratory.

Also, the role of the laboratory director, which is a requirement under CLIA, is not a familiar concept in the IVD world.

And finally, the concept of clinical consulting, which is also a requirement of a CLIA lab, has little or no precedent in an FDA-regulated environment.

To resolve the potential for getting caught in between two different, but necessary, quality systems during inspections, I recommend that CLIA and FDA jointly develop a formal plan defining roles, responsibilities and areas of focus during inspections of companies and laboratories offering LDTs.

Towards this end, I recommend that FDA focus on manufacturing processes with the recognition that reagents and instruments will be used by a single in-house customer.

I recommend that CLIA focus on laboratory services and testing processes, in particular, test ordering, results delivery and interpretation of results.

And finally and perhaps most importantly, that

CLIA and FDA jointly develop a common language for areas of quality systems overlap and develop and use inspectors trained and knowledgeable in both quality systems.

My second concern from the perspective of an early adopter of the IVDMIA draft guidance is that following 510(k) Class II Clearance, additional instrumentation that would be needed by the lab requires submission and clearance of a special 510(k).

Although I understand to an extent the FDA rationale behind this decision, since many reference labs are using instruments not manufactured under cGMP, the requirement appears overly burdensome.

Towards this end, I recommend that FDA eliminate this requirement for a special 510(k) prior to implementation of additional instruments as long as the newly acquired instruments demonstrate equivalent functional performance compared to the originally cleared instruments and that they have been qualified and validated to the same standards as those original instruments.

Finally, a note of thanks to FDA for holding this public forum today and giving all stakeholders a chance to air their concerns and views and recommendations for improvement and

we all share the same goal in terms of patient safety. Thank you.

MS. SERRANO: Anna Longwell will be our next speaker.

MS. LONGWELL: Hello. I'm Anna Longwell and I'm an attorney practicing Food and Drug Law in California. I'm a Member of the California Bar and the U.S. Patent Bar. My clients include companies on both sides of this issue, so I want to tell you I'm speaking for myself and myself alone in this presentation. And I will be sending a more detailed presentation to the docket.

Currently, the challenges faced by laboratories providing clinical diagnostic information are compliance with CLIA and the state requirements to provide high quality information to clinicians and being able to understand and respond to FDA's position on their role in regulating LDTs.

At the same time, the challenge faced by diagnostic manufacturers providing advanced technology IVDs is one of competition by what they perceive as a less regulated provider. They perceive LDT providers as able to make claims that require less validation than manufacturers would have to provide for the same indications.

So thank you for sponsoring this meeting. It is my hope that this meeting is the final step in a long and confusing

sequence of events, starting with publications of the ASR rule in '97, well before the publication of the draft IVDMIA guidance in 2006 and including the recent untitled letters to providers of genetic information stating that they were manufacturing a medical device.

My suggestion is simple. It is time for notice and comment rule making to take place.

FDA's published overall strategy for regulating laboratory-developed tests should take the form of an NPRM. This approach would give FDA the chance to expand and explain their assertion, but since they have legal authority to regulate commerce and medical devices and laboratories of LDTs are producing, employing and possibly marketing medical devices, that they have authority over these laboratories.

Simply answering the question exactly what is being regulated would be an advance over the current situation.

This NPRM could address the multiple questions now being asked by providers of LDTs, such as how would 21 CFR Section, say, 20 apply to LDTs, in particular, the design control requirements?

Are LDTs classified by FDA in terms of risk as Class I, II and III? How would this classification take place? What is

required labeling for an LDT since it may not be what is described in 21 CFR 809?

What are required reporting requirements for LDTs, Sections 803 and 806? And there are numerous other compliance issues ranging from validation of new lab equipment not mentioned in the pre-market submission to registration and listing and possibly other regulations, such as the Humanitarian Device Regulation.

Continuing to regulate on a case-by-case manner is contrary to the public interest and contrary to the traditions of open availability of legal requirements and equal treatment under the law.

The Administrative Procedure Act is very clear on the legal expectations for agencies and it is difficult to see how FDA can consider this issue exempt from the requirements of rule making.

I cannot describe such rule making as impracticable, unnecessary or contrary to the public interest and, therefore, exempt from the requirements of rule making.

If a public health emergency exists, it has yet to be well-defined. And FDA's current approach of informal communication with individual LDT providers seems to indicate

that no such emergency exists.

Regulation binds the regulator as well as the regulated guidance does not. Therefore, my suggestion for clarification is to resort to what appears to be a requirement for resolution of the issues before the Agency and those currently facing providers of LDTs.

Give us a role, please. Thank you.

MS. SERRANO: Our next speaker will be Kathy Hibbs.

MS. HIBBS: Good morning. I'm Kathy Hibbs of Genomic Health, a CLIA-certified laboratory providing advanced diagnostics to physicians using -- treating breast and colon cancer patients. Thank you for the opportunity to speak on the challenges facing clinical laboratories, particularly in regards to the potential changes to the regulatory requirements.

Many recognize the crisis in health care and the role that clinical laboratories developing personalized medicine tests like Genomic Health play in addressing this issue.

This morning I will highlight Genomic Health's approach and progress in breast cancer and our view that any additional oversight of highly regulated laboratories, such as ours, must be balanced with the critical need for further innovations

and patient access.

400,000 patients worldwide each year are diagnosed with early stage breast cancer. Historically, most would have been offered chemotherapy, even though only four out of 100 with no negative breast cancer would benefit and all would suffer the side effects.

The ability to provide information to better guide treatment decision and avoid toxicity and side effects for patients can help manage unsustainable costs to our health care system.

The Oncotype breast cancer test which provides a prediction of an individual patient's relative risk of their cancer's recurrence and the potential benefit for chemotherapy was launched in 2004 in compliance with federal CLIA Regulations and CAP accreditations.

I really want to highlight this morning that the tests in these claims have been rigorously studied and reviewed and over 13 studies in 4,000 patients. Importantly, these results have been widely published in peer review journals, including the New England Journal of Medicine and the Journal of Clinical Oncology.

In addition to publications, Oncotype DX has been reviewed for and included in published breast cancer clinical

guidelines. Oncotype DX has also been reviewed by numerous public and private expert panels, including New York's Clinical Laboratory Evaluation Program and Blue Cross/Blue Shield's Technology Evaluation Center.

To date, over 8,000 physicians have ordered this test for more than 150,000 patients worldwide and it is widely covered by insurance and Medicare.

I highlight this to make the point that any additional regulation of laboratory- developed tests must recognize the value the validated tests, like Oncotype DX, are already providing to patients in the health care system and carefully balance the risk posed by the use of this test information by physicians with the risk that such regulation will stifle needed innovation necessary to improve patient health outcomes.

It is essential that the Agency carefully address the evidence requirements for additional validation of laboratory tests, so that labs have a clear path for clearance of such tests, based on the relative information. And in order to provide meaningful claims to physicians that use these tests in making treatment decisions.

We look forward to working with the FDA and other stakeholders to review the possible development of a new

regulatory framework that both supports innovation and meets the needs of patients. Thank you.

MS. SERRANO: Our next speaker is William Clarke.

DR. CLARKE: Good morning. I'm Bill Clarke and I am a Clinical Chemist and Laboratory Director for Johns Hopkins Hospital. I'm here today representing the American Association for Clinical Chemistry.

My comments are on behalf of the association only and are not representative of any Johns Hopkins entity.

AACC represents professional clinical laboratory scientists that include MDs, PhDs and medical technologists. Their members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigation and work in hospitals, independent laboratories and the diagnostics industry worldwide.

AACC appreciates the opportunity to provide input to the FDA regarding the Agency's oversight of laboratory-developed tests. We support the dual goals of insuring that patient testing is accessible and accurate. We recognize the challenge also that the Agency faces as it attempts to find the appropriate regulatory balance between patient

protections and scientific innovation.

We welcome the opportunity to work with you in developing policy in this unchartered territory.

Now, although the purpose of this meeting is to discuss the appropriate level of FDA regulation of LDTs, we do believe it is appropriate and important to acknowledge that these tests are already subject to vigorous public and private sector oversight.

All laboratories performing LDTs are categorized as high complexity under CLIA '88 and are therefore subject to stringent personnel, quality control and proficiency testing standards among others.

In addition, CLIA laboratories must document the analytic validity of LDTs and make that information available to the inspectors. Many of the laboratories conducting LDTs are also credited by the College of American Pathologists, one of the leading private accrediting bodies in the nation.

CAP requires testing facilities in their Laboratory Accreditation Program to demonstrate the analytical validity of LDTs as well as document how they are clinically validated. There are also state requirements in place.

As previously mentioned, one example is the New

York State Clinical Laboratory Evaluation Program that requires laboratories to document analytic and clinical validity prior to introducing a test.

These standards apply to all laboratories conducting testing on patient specimens derived from that state, thus, AACC believes the regulatory gap that needs to be addressed is very narrow.

AACC supports the FDA's idea of employing a risk-based classification approach for determining the level of oversight for LDTs. We believe the categories within this scheme should be high, moderate and low with the degree of regulation associated with each category determined by the level of risk to the patient.

An example of a high risk test would be an assay where clinical validity cannot be independently verified. For example, IVDMIAs. We urge you to consult clinical laboratories as you construct any risk stratification scheme.

Now, once the risk stratification occurs, AACC recommends that high risk LDTs be subject to FDA oversight, whereas low and moderate risk LDTs should be regulated by CMS along with CLIA '88 Regulation.

We believe it is important to note that a test

defined as a high complexity test is not necessarily high risk. In fact, we would expect the vast majority of LDTs, which are well-characterized, to be associated with low to moderate risk.

AACC also supports a special exception for orphan tests. Unless a limited exception or other accommodation is made, no one, neither a manufacturer or a clinical laboratory will develop these critical tests for diagnosing and treating rare diseases.

To finish, we would like to thank the FDA for the opportunity to comment and we look forward to working with you on this issue.

MS. SERRANO: Liz Lison will be our next speaker.

MS. LISON: Good morning. My name is Liz Lison. I'm an Independent Regulatory Affairs and Compliance Consultant working predominantly with emerging diagnostic companies, many of which use LDTs as part of their business model.

My presentation today is based on my own observations and my own opinions and does not necessarily represent any actions or opinions of my clients.

I want to highlight two specific challenges many

clinical laboratories raised when considering FDA-clearance or approval: The implementation of the quality system regulation and generating data for an FDA submission.

And then outline a possible solution for regulation of LDTs by the FDA. Both new and established CLIA labs confine the QSR confusing. Most can't see how it applies to clinical laboratory testing and they often think they have to have two separate quality systems.

The concept of design controls is usually new to the laboratory and is often cited as the major reason why they can't implement the QSR.

The initial response tends to be that the QSR is so different from the CLIA requirements. It will be too time consuming and expensive to follow both. Despite the common goal of patient safety, the CLIA Regulation and the QSR are two quality systems separated by a common language.

As we know, verification and validation means something very different in each system. However, if you examine the two systems closely, there are many common areas and I have yet to find the progressive clinical laboratory that can't build an effectively implemented single quality system to meet both regulations, including the dreaded design controls.

The difference in data requirements between a clear validation and an FDA submission means that laboratories often see the clearance or approval process as the too time consuming and extensive. Although the performance criteria for the analytical validation is similar for both, laboratories often lack familiarity with the consensus standards recognized by the FDA and perform studies for CLIA, which would not be acceptable to the FDA.

Clinical validation isn't required by CLIA and laboratories who perform clinical studies often have limited understanding of study design and lack adequate statistical support.

Perspective studies are time consuming and expensive and often bank samples can provide bias data sets and may have issues with sample integrity. So when the pressure is on from the competition, the management or the investors is all too easy to launch an inadequately validated and out of control test system.

Inadequate oversight of the current system makes it almost self-regulating. Unlike many self-regulating systems, the actions of some eventually spoil it for everyone.

The future regulation of LDTs should leverage the

expertise and current infrastructure of the IVD and not cause duplication of effort or create more review bodies.

However, the current clearance and approval approach that is available to the FDA may not be the best way to regulate LDTs. If emerging diagnostic companies continue to innovate and facilitate the growth of personalized medicine, any new approach will have to be easier, faster and less expensive.

One possible solution is an initial FDA authorization for LDTs. This could be based on the emergency use authorization recently used for the H1N1 tests. A low regulatory bar with a fill-in-the-blank submissions and faster review times would allow companies to market their tests for a predetermined time period, which could be based on risk.

During this period, the lab could build on the data submitted for the authorization to obtain clearance or approval. The advantages of this type of authorization approach by the FDA include the independent review of performance data which will prevent the truly awful LDTs reaching the market.

It will provide visibility of who is offering what tests and a mechanism for monitoring post-market issues using the currently available systems.

And importantly, it will allow the laboratories to

establish clinical utility and reimbursement while continuing to work towards a clearance or approval.

Our common goal here is to find a way for patients to access safe and effective tests and advanced personalized medicine. As we work through the possible solutions, we should ensure that we do not place the responsibility for determining safety and effectiveness of the test on the patient by requiring them to search through databases and interpret validation data or even worse identify a physician that is doing all of them.

In summary, the current system is weak and poorly performing tests are getting onto the market. I believe an FDA authorization approach would provide the right amount of FDA oversight and go a long way to rectifying the situation without stifling innovation.

Thank you for the opportunity to comment.

MS. SERRANO: Our next speaker is Klaus Schafer.

DR. SCHAFER: Good morning. I'm Klaus Schafer, President and CEO of TessArae, LLC, a small biotechnology company, located in Potomac Falls, Virginia. And I wish to thank the FDA for the opportunity for allowing our small company to

express our views in this public forum.

TessArae is not a company that markets classic biomarker-based diagnostics. We do not design or sell expression arrays. We are not a lab service company with its own CLIA lab. In fact, we prefer not to create or maintain a CLIA lab letting other better equipped and trained groups provide that function.

We are not purveyors of direct to consumer diagnostic tests, preferring to work with qualified medical and laboratory professionals.

So why are we here and why are we even interested in this whole topic of LDTs? TessArae's business is designing, developing and distributing high performance targeted gene sequencing microarrays, their associated reagent kits and real-time data analysis of assay-generated DNA sequences.

These direct sequences can reveal specific DNA mutations and inherited diseases and can reveal the presence and identity of one or more pathogens causing infections.

We take known gene sequences and mutations on array and look for underlying sequences in the target sample to determine the presence or absence of mutations.

We design or test to meet the specific

requirements of individual clients like university medical centers, government or commercial CLIA labs as customers. Because we deal with direct sequencing, this is the basic sequencing, we may seem a little unusual in a fit for this audience. Yet, only gene sequencing directly and unequivocally detects and identifies specific mutations or pathogens whether from whole genomes or targeted genes and their associated mutations.

Today in contrast, most nucleic acid testing devices use only short signatures of gene sequences as indirect biomarkers of intended target gene mutations or pathogens. These tests cannot differentiate it among similar sample gene sequence signatures that may represent the intended target or even unintended targets.

These are also the typical IVDMIAs which have become the direct to consumer genetic tests. TessArae technology and any other highly multiplex direct targeted gene sequencing platforms overcome the striking and sometimes costly shortfalls of conventional approaches to molecular diagnostic testing.

This leads to our dilemma in that the current regulatory path for diagnostic tests through OIVD is simply not congruent with the superior capabilities, performance and

informational value from highly multiplex direct targeted gene sequencing devices.

The current pathway ensures that technical advances will only be congruent with status quo capabilities of previously approved devices. This is exactly why TessArae is here. We heard yesterday when an audience participant asked about the position of the FDA regarding genomics sequencing devices, there was simply no answer from the panel members other than we will have to study it further.

Under current regulatory policy, highly multiplex direct targeted gene sequencing assays developed by manufacturers face an impenetrable barrier to FDA-clearance for clinical diagnostic use.

On the other hand, assays can be developed internally as validated tests or LDTs by highly competent CLIA or CAP labs with little regulatory oversight. However, these tests might be developed with little or no involvement from commercial entities like ourselves that develop technology and maybe the real subject matter experts.

The critical point is whether or not individual laboratories must be solely and exclusively the innovator and developer and validator of any new test to be offered as an LDT.

Some laboratories are, therefore, reluctant to work with us, with any third-party vendors like us, and others are willing to work with us and so it creates confusion.

Because the definition of LDTs remains unclear, some CLIA labs really will work with us and like I said, some won't. The labs that will not work with us fear regulatory retribution that may affect the laboratory's accreditation, not just the implementation of a particular test.

Legal counsel regarding this subject likewise is cryptic and inconsistent and it seems these groups typically understand the traditional pathway regulatory channels.

As a constant, we believe that we should be able to sell our experience to CLIA or CAP laboratories for tests we develop in collaboration with these labs very much in the way consultants with special expertise support all of us.

We are an original equipment manufacturer operating much like a contract research lab to a drug development company. CLIA labs neither have the time, resources nor skill set to design and develop our type of custom design direct sequencing test without our help.

They lack the bioinformatic skills and wetware and have been and have not been trained in these areas.

So what we would ask of the FDA, we strongly encourage them to allow individual testing laboratories to accept -- access to third-party commercial products and our services and support of LDT development as part of their validation protocol and would require appropriate assurance of availability and configurational reproducibility for third-party components or services.

So we do ask for the FDA to allow third-parties like us to work with these large CLIA labs. Thank you. Those are my comments.

MS. SERRANO: Our next presenter is Frank Cockerill.

DR. COCKERILL: Well, I first would like to thank the FDA for allowing us to present today. My name is Frank Cockerill and I'm Chair of the Department of Laboratory Medicine Pathology at Mayo Clinic. A very large academic department.

As well, I'm President and CEO of Mayo Medical Laboratories which services around 4,000 medical centers around the world with a number of LDTs, very unusual tests with low volumes. And we will get into more detail about that in a bit.

I'll have some general comments and then specific comments. I must also be transparent in that I do chair

the Microbiology Devices Panel for FDA. And I do appreciate all of the sincerity from the FDA perspective regarding safety with the testing that we do for our patients.

To meet the clinical needs of Mayo Clinic patients and more than 4,000 additional medical centers that we serve worldwide, our practice has a large and diverse test menu, including numerous LDTs. Due to their limited commercial appeal, most of these important tests would not exist if it were not for dedicated test development activities by our organization and many others like it around the country.

To be blunt, basically a lot of the tests that we do that are LDTs will not be commercialized. They are expensive to do. There is not a great return on the investment.

For any new oversight of LDTs to be successful and efficient, there must be coordination among all government agencies involved with the laboratory industry.

Currently, laboratories must meet the compliance requirements and we have heard this over and over again, CLIA, various accreditation agencies, including CAP and state-specific regulations and most notably, that's New York State.

We have talked and heard about level playing fields with IVD industry. In all due respect for our IVD industry

colleagues, they do not have to deal with additional regulatory agencies like CLIA, CAP, New York State, et cetera.

So adding additional regulations through FDA will add to that burden that we experience, which makes for maybe an even less level playing field.

Any new regulations should provide a single set of requirements to reduce redundancy and ultimately cost. Conversely, adding more layers to the current regulatory structure would further complicate the approval process, resulting in a greater strain to the laboratory industry.

However, if implemented correctly and in partnership with other regulatory agencies, new regulations through the FDA could streamline expectations while increasing value in patient safety.

We believe any new LDT Regulations must clearly define a fair, equitable and standardized design and development process, which a lot of us aren't quite certain about what actually the process will be.

Furthermore, this process must be efficient, timely and not significantly raise the cost of development. A process that results in higher costs would severely impair the development of lower volume assays making these uneconomical

to develop and ultimately limit patient and physician access to these important tests.

Many laboratories offer LDTs that identify only 10 to 20 affected patients each year and we are one of those. Although these tests have very low volumes, the clinical information they provide can be life saving. Access to tests like these is critical to preserve patient safety and must be taken into account when regulating LDTs.

A very key aspect of any new regulations and there were a lot of questions about this yesterday, is what is the definition or the level of clinical validation that FDA will impose?

Currently, we know that CLIA requires analytical validation of performance characteristics of LDTs. I would challenge the FDA to critically look at clinical validation approaches and are you innovative in your approach towards what is adequate validation from the clinical perspective that adds safety to all of these tests?

And there are studies out there, there are papers that are looking at more of a real-time approach towards these sorts of clinical evaluations.

In summary, to be a bit prescriptive, any new oversights should be consistent with the following expectations,

be based on reasonable stratification of risk, that's going to be a challenge to define, accommodate innovation to meet the growing needs of clinical practices, avoid redundancy with current regulatory agencies, provide regulatory agencies the appropriate staffing and that's the FDA.

You really need to have the appropriate staffing to take this on. Establish a fast-track for tests to address emergency situations, especially infectious disease related. And H1N1 is an example of that and we had the privilege to work with the FDA and a third-party IVD company with the Anthrax test that you helped us with a few years ago that you really moved very quickly, and allow for provisional use of LDTs with appropriate disclaimers where there is limited access for clinical validation.

Now, we heard about IDEs. There are some issues there related to consent, getting consent from patients is not always an easy thing to do. Processes would have to be developed to accommodate that.

With that, I thank you for your attention in listening to our proposals.

MS. SERRANO: Our next speaker is Paula Revell.

DR. REVELL: Good morning. My name is Paula Revell and today I'm representing the American Society for

Microbiology.

ASM will submit a complete statement to the docket, but today I will present an abbreviated version.

The ASM strongly supports oversight of LDTs and believes that existing regulation provided by CLIA when appropriately applied accomplishes the goal of oversight through proficiency testing, personnel standards and quality systems, which includes the verification of validation processes.

For the purposes of this document, verification is defined according to the terminology used by CLIA. It is the one time process to determine or confirm LDT performance characteristics prior to the beginning of patient testing.

There is no doubt that certain patient populations are threatened when the LDT has not been appropriately verified. However, an appropriate balance of oversight is necessary so as not to impede access to important LDTs that continue to aid in the diagnosis and treatment of rare, new and/or reemerging infectious diseases.

Laboratories depend on LDTs to readily and rapidly respond to emerging infectious disease outbreaks such as H1N1 and SARS to measure viral lodes, to detect changes in antimicrobial susceptibility patterns or to test for diseases that do

not have commercially available diagnostic tests, such as herpes simplex virus in the CSF, all of which greatly assist physicians in the appropriate care and management of their patients.

ASM feels strongly that additional FDA oversight will result in time delays that will negatively impact patient care. Additional steps to strengthen regulation will require many hospital laboratories to increase the volume of send out testing to reference labs resulting in a time to result that exceeds clinical relevance for patients and physicians as well as an increase in cost to the health care system.

Publicly funded or smaller laboratories will be at a disadvantage due to limited resources. In addition, potential fees associated with the submission process may compete with resources needed to perform the actual verification.

This financial and time burden is not feasible for a large number of laboratories and may result in only the largest and perhaps commercial laboratories having the ability to offer LDTs. Furthermore, duplication of requirements for verification will likely drive up costs to consumers.

In summary, additional FDA Regulation is likely to be prohibitive for many laboratories including academic and hospital-based labs.

ASM recommends that the FDA and CLIA-approved laboratory accrediting organizations work together to enhance the CLIA inspection process with respect to verification to ensure that LDTs are safe and effective and that patient care is not threatened.

Some suggestions are as follows:

Create a new LDT inspection checklist and/or add items to current checklists with clearly defined expectations, rather than leaving it up to inspectors who interpret differently and many of whom have little, if any, experience with LDTs.

Establish clearly defined requirements for the verification and validation of LDTs.

And clarify the appropriate use of alternate sample types for uncommon analytes. However, careful consideration should be given to those LDTs that assist in the diagnosis of rare diseases, because the absence of significant number of positive samples could make verification of assays that detect these diseases impossible if the same verification requirements are applied to such tests.

Establish essential requirements for acceptable sample and reagent stability for determination of acceptable limits of detection and acceptable assay performance parameters such

as analytical and clinical sensitivity and specificity and intra-assay reproducibility.

These same standards need to be established for quantitative assays as do requirements for limits of quantitative, linearity and reportable range.

Establish essential requirements regarding specimen collection and rejection criteria, reagent preparation, acceptable control types and limits and proficiency testing.

Additionally, ASM believes it is important for the FDA to develop a risk stratification framework for LDTs. Risk stratification would likely be based upon the impact of an incorrect patient diagnosis attributed to the LDT results and/or the potential for disease transmission due to failure to identify a communicable pathogen.

Due to the complexity of risk stratification, ASM recommends that the FDA seek input from clinical experts and laboratorians if they elect to develop this framework.

Finally, the ASM is concerned about the FDA's current resource base, including adequate number of staff, level of expertise and available funding to oversee and enforce stricter LDT Regulation in an expeditious manner.

If additional oversight is mandated, the FDA

should consider creating an expert panel to assist with enhanced oversight process, careful examination of existing models, such as New York State's LDT oversight process, might provide insight into whether additional regulatory steps and standards have improved quality and safety or if the additional steps have simply slowed the process.

On behalf of ASM, I thank you for the opportunity to comment.

MS. SERRANO: Our next speaker is Phoebe Mounts.

MS. MOUNTS: Thank you. Good morning. I would like to start by thanking FDA for hosting this meeting. I think the size and diversity of the audience is a very clear indication that this is a very important topic for many stakeholders and we all welcome the opportunity to discuss these issues.

I would like to start with my disclaimer slide. My opinions expressed in the presentation are my personal views. They are informed by a prior career as a laboratory scientist and I have enough gray hair to put myself in that camp of those individuals who performed in situ hybridizations and immunohistochemistry assays. And I welcome real-time PCR.

The advances that we have made in the

technology is really astounding and I think we all appreciate and welcome the sensitivity and specificity of the assays. So my views are not the views of our clients or my partners at Morgan Lewis. But my views are informed by trying to counsel my clients, who are working with LDTs.

So I thought it was important for a five minute presentation to really try to distill the issues down as much as possible.

So these are terms that FDA has heard many times, but one problem that I see very often is that the Agency's policies on LDTs are not transparent. When there is a policy of enforcement discretion, it is not clear to those of us on the outside what the policies are.

So I would welcome some change from the Agency in trying to articulate what the policies are for LDTs. And I know the Agency has been very good, especially CDRH at issuing guidance documents and we welcome those guidance documents. We find them enormously helpful.

In the absence of guidance documents, we go to untitled letters and warning letters. And I know guidance documents take a lot of time and effort, but it really is a very efficient way of communicating the Agency's views and policies to

a vast number of stakeholders. So I think that's a very important issue.

I think a lot of the issues we have been discussing about LDTs lack clarity. I listened yesterday very carefully for a definition of an LDT and did not hear it.

I have always thought that the statutory definition of a medical device, including the term contrivance, would allow us to capture just about everything, but it does not, in my opinion, capture business model. So I think if we have to resort to talking about business models for LDTs, we are not on the right pathway.

And then finally, a problem that I have experienced is inconsistency. In the absence of guidance documents or clear policies from the Agency, I frequently encounter clients who have derived the position based on an informal discussion with people in OIVD and I cringe, because I know those opinions expressed were done at a meeting or an informal context and therefore not going to carry the weight that a company should be able to rely on.

And I think it is important to know now that the LDTs are not without oversight and I would encourage the agency to start with the current policies and the current oversights in

place and modify those to make sure that they address the problems.

I think CLIA certification and the inspection by CLIA is clearly a very important place to start. The Agency, FDA, has a lot of experience doing inspections. They have got a well-oiled machinery that does a lot of inspections. I think having FDA's inspection team work with CLIA would address many of the issues we have been talking about.

We have got regulatory framework in place for analyte-specific reagents. We can work with that framework and improvement. And I think I was a little disheartened yesterday to hear some of the derogatory comments about physicians and hospitals ability to be involved in the oversight process.

I think we have got a lot of intelligent skilled people out there and should be involved in the process.

So any change in the current status for LDTs needs to be derived from a transparent process. This meeting is an excellent first start and I would encourage the Agency to continue the dialogue and make sure that all the stakeholders are involved in the process.

I think it is very important, as many speakers have said, that any change does not or should not be burdensome for

either industry or for FDA. FDA has limited resources, so does industry. We are in very economically challenged times. We don't need additional costs.

Any change needs to be implemented over a reasonable period and I suspect, based on the comments and the diversity of opinions expressed over the past two days, it's going to take some time to arrive at a new framework for improvements in the current framework. So I think we are going to need an equally long time to try to implement any changes.

Importantly, any change in status should not be restrictive for innovation. And by that, I mean, it should accommodate revolutionary and evolutionary changes in the technology. We shouldn't be wedded in what we have now. We should look ahead and say what we put in place should be sufficiently flexible and would address the technologies down the road.

And then finally, we should be concerned about not adding any unnecessary costs to health care.

MS. SERRANO: Michael Ryan will be our next speaker.

DR. RYAN: Good morning. My name is Michael Ryan and I'm speaking on behalf of the New York State

Department of Health. As Director of the Wadsworth Center's Division of Laboratory Quality Certification, I work closely with the Clinical Laboratory Evaluation Program and the Scientific Staff of the Wadsworth Center on all aspects of the oversight of laboratory-developed tests.

Laboratory-developed tests require review by our program and only assays that we determine to be both analytically and clinically valid receive New York State approval.

We have seen a wide variety of submissions including those using more common methodologies to assays using more complex state-of-the-art technologies, such as the multi-component genetic test now being introduced for personalized medicine.

Given our active involvement in this process, it is clear that we do support the oversight and review of LDTs.

Our experience in the review of LDTs provides us with a unique perspective on the many challenges faced by clinical laboratories that are seeking approval for use of these types of methods.

I would like to take this opportunity to describe some of these challenges to you and ask that you consider them as you debate taking steps to oversee LDTs.

Any assay not expressly approved, cleared or exempt by the FDA, including commercialized test kits, variously labeled as RUO or IUO are subject to review by New York State.

In addition, FDA-cleared/approved tests that had been modified from their intended use must be reviewed. Labs seeking approval for an LDT submit validation packages to the Clinical Laboratory Validation Program. Packages are reviewed by Wadsworth Center scientific staff.

The scope of the reviews that we perform on LDTs includes assessment of laboratory standard operating procedure manuals, the approach used for method validation and data from validation studies.

It has been our experience that laboratories often need guidance on the type of information that needs to be included in the SOPM and what steps need to be taken to properly validate an assay. We have seen instances where SOPMs are not well organized or incomplete and laboratories often confuse or misuse the terms analytical sensitivity and specificity and clinical sensitivity and specificity.

To assist laboratories, New York State has prepared submission guidelines that describe the requirements of an SOP in a validation study. The guidelines describe the types of

assays that require approval and a checklist of items that need to be included in the SOPM and validation study.

Additional information is also requested, such as supporting literature, marketing materials supportive of the literature and the laboratory's served population and example reports with standard elements and patient-specific interpretations.

In several scientific areas, there are specific requirements that need to be fulfilled. For example, guidelines have been developed in the area of molecular microbiology that cover a variety of techniques, such as those used for the detection and/or quantitation of infectious organisms by real-time PCR and speciation of organisms using DNA sequencing.

All of our guidance documents are available on our website and we are working to establish a web-based system that will allow labs to submit validation packages online.

Our ultimate goal is to make the submission process easier for the labs. With this in mind, we must consider the fact that laboratories large and small operate in a market-driven climate. Tests change rapidly and others become obsolete.

This is quite evident in the area of genetic testing.

An approved method may be expanded to include more coverage of a gene or in a number of genes offered in panels. While changes in the assay often result in very small increases in detection rates, the test is more comprehensive and the laboratory would need to obtain approval before using the assay.

We appreciate the fact that these types of modifications in the assays are inevitable. However, regulatory agencies must be willing and able to accommodate the ever-expanding market.

I would like to emphasize once again that New York State supports FDA's oversight of LDTs. However, we are very concerned that if all the LDTs are treated in the same manner as IVDs, there will be untoward consequences for state public health labs as well as for the many academic, clinical or commercial laboratories that are at the forefront of developing LDTs.

Such a move would essentially limit the development of new assays to the large commercial labs and manufacturers who can afford the costs associated with such an extensive approval process.

This would raise the cost of diagnostic testing for all users. It would also limit the diversity of available assays to

those for which there are large enough markets to justify the cost of development.

Further, we do not see the necessity for applying some of the IVD requirements to LDTs. For example, the requirement to test assays at multiple sites does not deem relevant for an assay that has been developed for use in a single laboratory.

Additionally, laboratories developing LDTs, almost by definition, have experienced scientific staff capable of assessing reagent quality. Whereas, those receiving commercial IVD assays from the manufacturers may not.

We would therefore also question the necessity of GMP conditions for all components in an LDT where they are not being manufactured for subsequent distribution to numerous less experienced laboratories.

The FDA should consider their approach that will be used to administer the oversight of LDTs with an emphasis on making the process as streamlined for the labs as possible. We would also support the option of an abbreviated approval process or a process similar to the emergency use authorization provided for H1N1 assays to enable public health laboratories to rapidly deploy LDTs in response to critical health emergencies.

I thank you for the opportunity to speak to you today on this very important topic.

(Applause.)

MS. SERRANO: Elissa Passiment is our next speaker.

MS. PASSIMENT: Good morning. My name is Elissa Passiment. I am here representing the members of the American Society for Clinical Laboratory Science.

ASCLS commends the FDA in its attempt to try and frame the issues around LDTs and we agree with the Agency that there is a need these days to look at these tests and assays as potential medical devices.

We are not talking about, in our opinion and our members' opinions, the tinkering that laboratorians do on a regular basis in their laboratories. We have done this for ages. We are chronic at it and we will continue to do it forever.

But we are talking about a group of assays that are much more esoteric, much more complicated and whose clinical implications are far beyond what most laboratorians are able to validate.

The menu has grown to the extent that laboratorians do not have the resources or the specimens needed

to even validate it as they take it into their own laboratories. Typically, the information about sensitivity, specificity, predictive values, likelihood ratios, et cetera, is not available with these laboratory-developed tests that, I think, are the ones that FDA should be most concerned about.

So it sets the stage for potential misinformation for health care providers, for our patients and for the health-conscious public. The concept that the scientific community and clinicians will somehow be able to sort out the real science from the inaccurate supposes that we all have the opportunity and the resources to study the test development and the methods intensely enough to understand and guarantee patient safety, but that's simply not the case.

Also, the concept that time will determine what the clinical validity will be worked in the old days. It doesn't work today in the era of instantaneous information, of worried well who are constantly combing the Internet, of disease advocates who are constantly looking for the next answer to their illness and/or their syndrome and to individuals whose science has been relegated to what we see currently in our elementary and high schools, that barely makes them capable of balancing the chemicals in their swimming pools.

The benefit for all of us will be that we will be able to use each other's intellectual endeavorsm the new laboratory-developed tests, safely and effectively because we will understand, because there will have been some oversight and it is very, very necessary, because there is an urgent need to bring translational research to the clinical laboratories so we can provide it for our patients.

We urge FDA to look at the IVDMIA guidance that they wrote. There was a lot in the latest draft that was usable and applicable to LDTs. We want though that oversight to be practical, so that we are looking at a process that, first of all, they can handle as far as their staffing is concerned and their expertise, something that has a PreIDE Process in it that will all be user-friendly and facilitate the introduction of technology after advice and guidance without stifling innovation.

The clearer and more defined the process, the easier it will be to follow. We are proponents, but skeptical proponents of any risk stratification because we have noticed that risk stratification in classifying wave testing has not exactly worked the way we had hoped.

Any risk stratification model will have to include a determination of harm to the patient, based on the intended use

of the test and the consequences of an erroneous result. Any tests that claim to diagnose either specifically or by differentiation must be considered at high risk. And likewise, any tests whose results purport to determine or direct therapy must also be considered at high risk.

The challenges are going to be that laboratorians are not going to understand the terminology and the approval process of the FDA, and FDA is going to have to be a lot clearer about all of that.

And the turn-around time from the FDA is going to have to be a lot better than it currently or has been historically. Laboratories are going to need help understanding what the FDA needs in the way of data, designing of studies and the QRS system.

There will be no question that oversight can slow innovation: all the more reason that FDA should not try to cover the universe of LDT, but rather those that are of high risk. Diagnostics of rare diseases will always be a challenge and the FDA will have to make exception for that.

With the challenges facing us, ASCLS thanks the FDA for the opportunity to comment at this time. We offer our members' expertise as FDA proceeds down the road to finalizing some sort of process for those LDTs that need to be overseen.

Thank you.

(Applause.)

MS. SERRANO: Bruce Davis is our next speaker.

DR. DAVIS: Good morning. Well, of the many hats that I could wear today, the two that I'm going to select from are that of past president of what is now the International Clinical Cytometry Society and a board member of the International Council for Standardization in Haematology. And I thank the opportunity to address you on behalf of these organizations.

Now, both of these organizations are involved in education as well as definition of best practice of clinical flow cytometry. It's a small group because these are very specialized labs. But as you can see from the list I provide here, the role of flow cytometry over the last 30 years has actually been fairly extensive, evolving from initially being one of a sort of fancy cell counter, if you will, counting CD4 T-cells or fetal red cells for monitoring fetal maternal hemorrhage to its condition or state today where it is probably arguably one of the most important tools in proteomics, where we measure the products of the genes and RNA that you all are concerned about, both outside and inside the cell.

So you can imagine few of us had a few eyebrows

when this article came out, because it doesn't take a genius to realize that what affects the molecular diagnostic area is likely soon to follow and hit flow cytometry.

In fact, when you look at the risk-based model that was proposed, in fact, when you look at the high-risk group, there are a number of flow cytometric applications that clearly fit in that area with regard to selection of specific therapies.

And, in fact, more and more there are proprietary or hidden algorithms or computations involved in the interpretation of flow cytometric data.

And finally, the risk-to-patient issue certainly can be fit for flow cytometry because it directs the use of cytotoxic therapies and inappropriate use of Rh immune globulin in pregnant women and has an incredibly adverse outcome.

And if you consider health expense a risk, certainly, some of the therapies have significant cost on a yearly basis.

Now, our concern is that in reality, most of the activities done in a clinical flow cytometry lab are, in fact, LDTs. There are very few cleared assays that are utilized in clinical flow cytometry and the practitioners in this area would probably tell you these are the least challenging, least interesting applications

of this technology.

So the majority as it is applied particularly, say, to hematolymphoid malignancies is all involved, I still like the term home brew, but, LDTs or laboratory-specific panels that are developed and utilized based on the experience of the laboratorians in that particular location.

And as we all know, whether we are in industry or practitioners, there are significant barriers at least to the existing routes to the FDA clearance for flow cytometric assays, because it is in a rapidly evolving field, still there is a lack of clear consensus as to what the best panel should be for diagnosis, because in reality, there are several routes to the truth.

The technology itself is rapidly evolving. Those of us in industry would be very hesitant to develop, say, a three or four color assay knowing that in the two or three years down the road, that assay would be out-moded, because the technology now measures twice as many analytes with the same basic approach.

The interpretive nature of flow cytometry again makes it difficult to argue sort of a kit-based approach for many things. And the other thing is there is certainly no clear predicate device in terms of applications.

With regard to validation of flow cytometric assays, the approach is very similar to what you all consider in your soluble measurements, either in chemistry or molecular diagnosis.

However, there are some unique concerns and that's what we want to make sure are heard. Namely, we are doing cell-based measurements, not just something floating in solution. And there is a number of variables that have to additionally be taken into account. I won't go into great detail, just to say that cells are, in fact, heterogeneous.

So what do these organizations propose to do? We challenge the CAP to use the expertise in these organizations, more so if they are unable with current inspectors to go in and do the job properly.

At the last meeting at ISCH, a guideline project was initiated that will be chaired by myself and Brent Wood. And we further proposed to have a guideline come through CLSI providing guidance on validation for cell-based assays.

So any of you that are interested can contact one of the members and hopefully will add to the current publications that are utilized by the FDA and others for guidelines in this area. Thank you.

(Applause.)

MS. SERRANO: So at this point, we are going to just keep going right up to the 10:00 break. There is a speaker that is going to be inserted here, Elisabeth Houtsmuller. She is actually replacing Speaker 3, Diane Allingham-Hawkins.

DR. HOUTSMULLER: Good morning. I am Dr. Elisabeth Houtsmuller and I represent Hayes, Incorporated. Hayes is a health technology assessment and consulting company located in Lansdale, Pennsylvania.

I am here in place of Dr. Diane Allingham-Hawkins, who is the Director of the Genetic Test Evaluation Program at Hayes. She prepared our presentation. However, unfortunately, she is unable to attend this meeting due to a family emergency.

Hayes and its employees do not have any financial involvement with manufacturers of any products that are discussed at this meeting. Travel and work regarding this meeting has been funded entirely by Hayes.

And Hayes is an independent health technology research and consulting company dedicated to promoting better health outcomes through the use of evidence. And in order to evaluate new and controversial emerging health technologies, we analyze the best available evidence and provide in-depth rigorous analysis of relevant clinical research.

For our genetic testing program, the model that is used is the ACCE model, which focuses on four key factors of genetic tests in their evaluation. The first one is analytical validity, which refers to the ability of a test to accurately and reliably measure the genetic change of interest.

The second one is clinical validity, which refers to the ability of the test to detect or predict the clinical disease of interest.

The third one is clinical utility, which refers to the ability of a test to impact patient care and/or health outcomes, specifically morbidity and mortality.

The fourth key factor are ethical, legal and social implications that are important because they are safeguards and impediments that are considered in the context of these other factors.

Now, in addition to these four key factors, there are other considerations that we use. For example, quality of life issues, patient preference. Patients may prefer one test over another and sometimes that is related to quality of life issues. The cost of the test can be a relevant factor.

And finally, the future of a test, in other words, a test may currently not be viable yet, but does that test have the

potential to have a significant impact in the future?

And so for the evaluation of all of the four key factors and the other considerations, what we need is good quality or are good quality published data.

And one of the greatest challenges we face in the, Hayes faces, genetic testing program is the lack of published, good quality data. The lack of published evidence. And although all of the factors that I just mentioned are important, the one that is probably most important to the FDA and the laboratories is analytical validity.

And currently, no standards exist for the analytical validation of genetic tests. So it is not clear what constitutes sufficient evidence regarding these questions. For example, how many patients should be tested? How many controls should be included? Is there an acceptable false positive or a false negative rate? The answer to all those questions are currently being debated, but unknown. So it's our opinion that standards need to be developed for the analytical validation of genetic tests.

The FDA should work with CLIA, the CDC and the laboratories themselves to ensure that reasonable and effective standards are put in place. These standards should then be

mandatory for any genetic test that's used for clinical purposes and the lab should be compelled to publish the results of any validation studies to allow for appropriate peer review.

In conclusion, the knowledge of the genetic basis of disease has the potential to revolutionize personal health care. However, there is currently insufficient published evidence for the clinical application of most genetic tests.

The FDA has the opportunity to ensure the safety and efficacy of genetic tests by participating in the development of laboratory standards for the validation of new tests and making such standards mandatory for laboratory-developed genetic tests.

With that, I will conclude my comments. Thank you for the opportunity to speak. And any questions may be referred to Dr. Allingham-Hawkins, whose email and phone number are on this last slide. Thank you.

(Applause.)

MS. SERRANO: Okay. I think we are going to fit one more in before the break. So the next speaker is Dr. Gail Vance. Is Dr. Vance here? Okay. Thank you.

DR. VANCE: Good morning. I want to thank the previous speaker for introducing this topic and I'll let you know that I represent the College of American Pathologists this morning,

and we have been working on a proposal to clarify the oversight of laboratory-developed tests since approximately February of 2009.

The article that you saw published in our publication, CAP, today was of October 2009, when we were releasing some of the preliminary aspects of this proposal.

So let's see, all right. First, in the way of background, I wanted to introduce the College of American Pathologists as a professional organization that has a membership of over 17,000 board-certified pathologists. These pathologists reside not only in the United States, but also internationally.

The college also has developed and continues to operate two very important programs for insuring good test performance. And those are the Laboratory Accreditation Program and the Proficiency Testing Program.

Our Laboratory Accreditation Program is a CMS-approved accreditor with higher standards to CLIA. For example, in our molecular test or our molecular pathology checklist, we have a requirement for clinical validation of these tests.

We set our accreditation standards through -- they are formulated by experts in their specialty. Also, I should tell you that CAP accredits over 6,000 laboratories in the United

States and the majority of high complexity testing laboratories are accredited by the College of American Pathologists.

We also operate a Proficiency Testing Program, which happens to be the largest Laboratory Peer Comparison Program in the world. It allows laboratories to regularly evaluate their performance and improve the accuracy of their patient results and be compliant with CLIA.

We believe that the college and the FDA have shared goals and these are:

To assure that the tests being offered are both analytically and clinically valid.

That we should leverage our resources to assure patient safety and public health.

We should assure patient access to testing and continue to encourage innovation and improvement of laboratory-developed tests.

Here is how we view the current situation. You have the FDA, which holds authority over the regulation of test manufacturers and has stated that they have authority over all LDTs. Yet, you also have another regulatory Agency, CMS, for which the laboratories are responsible to for following the guidelines of CLIA.

So the laboratory-developed tests in this chasm are dead sea in between these two regulatory agencies which creates a lot of confusion, regulatory confusion and lack of clarity for labs who develop and perform these LDTs.

Therefore, we created this proposal to try and eliminate or clarify some of this regulatory confusion.

First, I will offer you a definition of what we consider a laboratory test. And I will tell you in defining this laboratory test, it wasn't necessarily self-determined. We did use language that you can find in FDA documents.

We defined the LDT as a test developed within a CLIA-certified laboratory that is used in patient management, has both of the following characteristics: The test is performed by the clinical laboratory in which the test was developed and the test is currently neither FDA-cleared nor FDA-approved.

The CAP approach to the oversight of LDTs includes:

That the oversight of LDTs should be strengthened through a partnership between CMS, the FDA and third-party accreditors;

That analytic and clinical validation of these tests require oversight and continued monitoring.

Oversight should be stratified based on risk and our approach recommends that the FDA target only those high risk tests.

The paradigm for our risk basis is as follows:

Low risk for the low risk tests. The laboratory would validate their tests, as they currently do, and place the test into service. The accreditor then would inspect the laboratory as it currently does today.

However, for moderate risk tests, the laboratory would validate and then submit that data for independent review to the accreditor.

For the high risk test, the laboratory would continue to validate, but send that validation data for review by the FDA prior to placing the test into service.

The principles of our classification are as follows:

Low risk, the test is typically used in conjunction with other clinical findings to establish or confirm a diagnosis.

The moderate risk, the test result is typically used for predicting disease progression and identifying whether a patient is eligible for specific therapy.

And a high risk test includes those tests that predict risk progression of disease or patient eligibility for specific

therapy and the test uses proprietary algorithms or computations such that the test result cannot be tied to the methods used or intra-laboratory comparisons cannot be performed.

My last slide. The path forward. We believe that the FDA must proceed in the following fashion:

First, the FDA should consider meaningful public engagement with affected stakeholders as you are doing today. And we thank you for this opportunity.

However, in the future, the FDA should proceed deliberately and incrementally and through the process of notice and comment rule making.

I would also mention that this is an abbreviated presentation. The proposal can be found in the CAP website at cap.org. Thank you very much.

(Applause.)

DR. GUTIERREZ: Okay. So now we will take a break. We will take a 15 minute break, so we will be back by 10:20 and we'll start again.

MS. SERRANO: Just one thing, we will actually start with speaker number 22, Shashikan Kulkarni, just so that everyone is ready. Thank you.

(Whereupon, the above-entitled matter went off

the record at 10:05 a.m. and resumed at 10:19 a.m.)

DR. GUTIERREZ: We have a lot to get through, so we're going to get going again. Katie?

MS. SERRANO: Hi. So actually, I misspoke. We are actually going to start with speaker number 21. I guess it would be Richard Naples. Just one second.

MR. NAPLES: Thank you and good morning, everyone. I'm Rick Naples. I'm the VP of Corporate Regulatory Affairs for Becton Dickinson & Company in Franklin Lakes. And on behalf of BD, we are very appreciative of FDA holding this meeting today and the opportunity to provide you with our thoughts on these important matters.

First of all, I just wanted to say that we share the goals of all gathered here today to ensure timely patient access to safe, effective and innovative diagnostics. New genomic and molecular diagnostic and flow technologies have the potential to unlock the advantages of personalized medicine.

However, today there exist two routes to market for these important tests. One for clinical laboratories under CLIA `88 and the other for IVD manufacturers under FDA requirements.

These two regulatory schemes have over the

years served the diagnostics industry and the public health well, but today need to be rationalized in light of these novel diagnostics.

If these schemes are, indeed, two sides of the same coin designed to protect and promote public health, then there must be equal measures of timely patient access and publicly available information on the safety and effectiveness of these tests.

As a result, BD supports the need for a risk-based regulatory framework that regulates all diagnostics to the least degree necessary to ensure safety and effectiveness.

We believe regulation of any diagnostics should also be based on risk associated with how the test result influences treatment decisions, not on who makes the test or where it is made.

However, we also believe it is absolutely essential to strike the right balance between ensuring patient safety and encouraging innovation. In order to strike the right balance, BD recommends that FDA adopt the AdvaMed risk-based approach to regulation of all diagnostics including LDTs.

In developing this proposal, AdvaMed built on fundamental, well-established, successful risk-based approaches

to regulation. The AdvaMed approach is modeled after those previously established by FDA, Division of Clinical Laboratory Devices, the forerunner of OIVD back in 1996 and was used to clear the backlog of pre-market submissions from the early '90s to handle that large bolus of products, much like FDA would need to handle a large bolus of lab-developed tests.

In addition, the AdvaMed proposal also incorporates contemporary principles of risk management in the international ISO Standard, ISO-14971, 2007.

Under the AdvaMed proposal, which you heard about yesterday from Janet Trunzo, risk is determined by four factors. How the test is used clinically. For example, whether the test is used as a pointer or a determinant of treatment.

The degree of novelty of the analyte, that is how much is known about it, as well as the technology of the test platform and the level of training and experience of the operator. These risks can then be balanced against any existing risk mitigation factors, such as peer reviewed literature, FDA experience with similar assays, FDA special controls or guidance documents and clinical laboratory controls, such as CLIA '88 and CLSI Standards, as well as user experience and training.

We believe if FDA adopts this approach for LDT

regulation, the majority of low risk, well-standardized tests would be exempt and this would allow FDA to focus its limited resources on the high risk novel test that the public needs access to.

In adopting the AdvaMed risk-based proposal for all diagnostics, we believe FDA should consider the following approaches in addition to foster innovation:

Develop a comprehensive program to promote the development of novel diagnostics. Such a program for IVD manufacturers and clinical labs could include the standardization of reagents, reference materials and repositories of well-characterized samples.

Emerging markers for low prevalence disorders could benefit from early FDA oversight of analytical performance while clinical validity and utility are still being reviewed and considered and developed in the clinical lab.

And for rare diseases FDA should adopt enhanced CLIA '88 oversight, adverse event reporting of LDTs in lieu of pre-market reviews to avoid patients being disadvantaged. And IVD manufacturers should also be able to avail themselves of HDE like provisions.

We believe overall that a combination of these approaches allows the FDA to focus its limited resources on truly

novel diagnostics and we look forward to working with the clinical lab community and FDA on these great challenges. Thanks very much.

(Applause.)

MS. SERRANO: Our next speaker is Shashikan Kulkarni.

DR. KULKARNI: Good morning. My name is Shashi Kulkarni. I'm the Director of Cytogenomics and Molecular Pathology at Washington University School of Medicine in St. Louis.

I have no financial disclosure. And all the opinions which I express today are solely mine and does not represent any professional organization or Washington School of Medicine.

And these are acquired through my experience as a board-certified clinical cytogeneticist operating a clinical cytogenetics lab.

So I thought I'll start with sharing our mission of my lab. The mission is to enhance the quality of clinical and molecular cytogenomic service first through the development and implementation of state-of-the-art technology to constantly improve patient care, education and clinical research.

I really want to emphasize here that it is a dynamic process which is work in progress.

So typically, clinical cytogenetics labs offer several tests, such as karyotype, which is really the first whole genome analysis tool, and chromosomal microarray, which is really the first ever significant benefit of human genome project and FISH.

We are dedicated to the development and implementation of all these techniques. We adhere highest standards established by College of American Pathology, American College of Medical Genetics and Clinical Laboratory Improvement Amendments.

LDTs are extremely crucial and important components in a cytogenetic lab. And these labs are typically run by ABMG, American Board of Medical Genetics certified professionals who have extensive training, expertise and knowledge in quality control, quality assurance and clinical interpretation to aid patient management.

All these clinical cytogenetics labs are extensively regulated by College of American Pathology. They are subjected to requirements of high complexity testing. And I'm thankful to the previous speakers who have already alluded to all of these.

One of the most important things is looking for

standards and controls in the labs and for the newer technology in clinical cytogenetics labs such as chromosomal microarray. We have established collaborative efforts to develop reference material leveraging the already existing excellent GeT-RM Program at the CDC.

And as you know, that reference materials are useful for development of new genetic tests, validation of new genetic tests, assay performance, test calibration, intra-laboratory comparisons and freezing proficiency testing samples.

So as far as chromosomal microarray are concerned, we have leveraged the GeT-RM Program at CDC, which is led by Lisa Kalman at CDC. And as you can see from this cartoon here, all the stakeholders are represented and utilize the existing cell lines from Coriell Cell Repositories.

We work with vendors and more than a dozen academic and commercial labs are involved in this. And we also include the patient advocacy groups like chromosome donation outreach, UNIQUE and we also work with government agencies.

So my thoughts are that current regulatory oversight ensures that all diagnostic tests performed are according to the strict established guidelines. And any further mandated FDA oversight will significantly hamper this translation of new tests

and thus hamper the patient care.

And as rightly pointed by all the previous speakers, it will stifle innovation.

So my proposal is that all cytogenetic LDT providers must be board-certified in clinical cytogenetics by American Board of Medical Genetics. Proficiency testing should be absolutely mandated. Strict adherence to practice guidelines should be followed, the ones which are put forward by professional organizations like American College of Medical Genetics and CLSI.

Professional organizations which have existing regulatory guidelines can facilitate continuing education, review of current oversight mechanisms.

And my plea to FDA is to, please, engage us. We are here in an honest way to contribute to this fantastic new development. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is Ted Snelgrove.

MR. SNELGROVE: Good morning. It's a pleasure to be here. I'm Ted Snelgrove. I am the Chief Commercial officer for a pre-IPO VC-backed start-up in Silicon

Valley, Crescendo Bioscience, another proud member of the Coalition for 21st Century Medicine. But I'm speaking today, primarily, on my own behalf.

I have been in commercialization of high technology products in the biotechnology industry on the west coast as well as products in the precise medicine space. I was the first commercial hire at Genomic Health and was involved in designing and launching the Oncotype DX assay and setting up the pricing strategy for that product.

I left in '07. I do not speak for that company and so I'm speaking for myself today. But I do want to make sure that people understand that my perspective is really from the person who is actually involved in communicating this to health care providers and helping them understand how to use this and have been regulated both in the biotech sector for over a decade and then having been in this sector, where we are at a CLIA environment, I think I have some interesting perspectives that might be useful.

First of all, like all ethical business people in these sectors, we are pro-regulation because we need regulation. We need a good cop on the beat to make sure that the fly-by-night operators or those who might come in and create bad examples,

as Liz Lison referred earlier this morning, we need somebody to make sure that the shady operators don't get a foothold.

And so I'll just start off by saying we agree with that and we think the FDA needs to help with that in some fashion. But we are pro-regulation, but we are pro-regulation that works. And some of us, I think, at least I'm speaking for myself, are concerned about some of where this may be headed.

So a couple of things to stress this morning. How risk assessments are performed. How intended use claims and test interpretation is handled. And the overall approach of the Agency to the field.

First with regard to risk assessment, the FDA is excellent at telling test developers the degree to which their tests fall short of perfection. So we know when we are not clairvoyant and the FDA can tell us that.

If that's the end of the analysis, then that's a problem because the real issue is what is going on in medical practice today. And I can tell you that one of my sister companies in an exchange with a senior FDA executive was told medicine is messy. That's not an FDA problem, that's your problem.

Well, honestly, it is an FDA problem. And when

FDA has that kind of attitude, it's difficult for industry to feel like we've got a partnership here. So I think they need to understand that medicine may be messy, but it's also an FDA problem, not just an industry problem.

I think that the issue about relative risk is important and if we don't understand how bad the status quo in some of these cases is, in fact, these tests that may be developed that aren't perfect may be significantly better than a randomness, but that's honestly what is happening in some of these medical settings as the alternative is randomness. Which doctor you ended up going to and which day of the week. And that's not the way medicine should be happening in the 21st Century.

I would encourage the FDA to look at the CDC EGAPP example as a way to kind of do it, but also a way not to do it. The CDC, I think, did an excellent effort to develop a program for evaluating new molecular tests in this field and did a pilot program called EGAPP to evaluate them for those not familiar.

But they did exactly what I described. They told how all the tests that were less than perfect. They did 14, I believe, analyses and all 14 were negative. In their process of developing their analyses, they excluded all industry-generated data as biased, but it turns out all the people who actually did

these analyses were contracted university health economists who viewed this as an exercise to audition for the grant money coming out of the Comparative Effectiveness Research Program and they, therefore, made sure that none of their assessments were positive, because they view that as the best way to audition for comparative effectiveness grants.

So this is a problem going forward. And that's actually the bias that really mattered in that analysis, not the bias that they were worried about. So there is an issue here that needs to be thought through.

Secondly, it's important that test results and analytic validity can be laboratory-specific. FDA recognizes this in the GMP Rules. They think that manufacture of products needs to be a facility that is centralized. They don't want drugs manufactured in every retail pharmacy for obvious reasons.

The same thing can also be true for central labs that run single tests, I would challenge all those in other kinds of labs to believe that they think that they could achieve the same level of quality or reproducibility or standardization in a lab that is doing many, many kinds of testing.

Also, information is a different kind of product, different risk, different specialized rule set may be important here.

Think about a restaurant and a grocery store. We buy food at both places. They are both regulated. But the grocery store, because I take the stuff back and make it myself, has a whole different set of regulatory labeling requirements than the restaurant, which is also regulated, serves me food, but the service is very different and it has also got higher margins. You don't hear the grocery stores complaining about the margins in the restaurants, because they have different businesses. If the restaurant wants to open a store to sell groceries at the front end, some do that. You can buy pies or some grocery stores open restaurants like Whole Foods, that's okay. It doesn't mean that you can't do both. So I don't see any rules preventing IVD manufacturers from opening CLIA labs if that's their choice, and I understand Novartis has recently announced they are going to open a CLIA lab. So information is a different kind of product. It may be merited a different kind of regulatory approach.

And I'm getting a little short on time, so I'll just quickly summarize by saying intended use for analytic validity, clinic validity, are appropriate. Clinic utility is too far and if CMS holds that standard against this industry, it's going to be a problem. If FDA and CMS aren't on the same page, that's a problem.

And finally, just to point out that FDA skills and

experience may need to expand here. There is no guarantee that the licensed drug experts always have the requisite skills. Optimal statistical methods for some of these data sets that are massively larger than things FDA is used to dealing with may come from outside health care. In Silicon Valley there are other data sets. And so I just think that industry should expect the FDA to evolve along with us and the FDA shouldn't try to push the industry back into antiquated regulatory frameworks. Thank you very much.

(Applause.)

MS. SERRANO: Kathleen Rao will be our next speaker.

DR. RAO: Good morning. I'm Kathleen Rao from the University of North Carolina at Chapel Hill, where I'm the Director of the Cytogenetics Laboratory. I'm also a member of the Board of Directors of the American College of Medical Genetics and I'm here to represent the college today.

The American College of Medical Genetics is a professional organization composed of biochemical, clinical, cytogenetic and molecular geneticists, genetic counselors and other health care professionals committed to the practice of medical genetics.

Fellows of the college are doctoral level physicians and clinical scientists who are board-certified in one or more areas of clinical or laboratory genetics practice by the American Board of Medical Genetics, ABMG, and American Board of Medical Specialties Board.

The gene test website hosted by NCBI currently lists 1,850 genetic diseases for which diagnostic testing is available. Most of these genetic diseases fall into the category of rare or ultra-rare diseases.

With few exceptions, manufacturers have not developed and marketed FDA-approved testing reagents for use in diagnosing these rare or ultra-rare diseases.

Financial incentives for developing reagents and performing clinical trials are not available to offset the high cost of good manufacturing practices in the 510(k) or PMA process in the very small potential markets.

It is important to note that drug development for rare diseases has been enhanced by orphan drug incentives extended to the drug manufacturers. This may be something to consider in developing reagents or tests for rare genetic diseases.

However, given the lack of incentives, this has left the task of developing tests for the majority of genetic diseases to

the high complexity CLIA-certified genetic testing laboratories.

These laboratories are directed by board-certified doctoral level clinical scientists. They participate in proficiency testing and rigorous laboratory accreditation programs through CLIA. CLIA exempts states and its deemed organizations. They adhere to CLIA-mandated standards and professional laboratory guidelines published by organizations like ACMG.

Many of these laboratories exist in major medical centers and serve the most severely affected patients and most vulnerable populations. The financial burden of requiring these laboratories to meet GMP and/or 510(k) PMA requirements along the lines of clinical trials for instance, in addition to their current regulatory requirements, would significantly reduce both the financial viability of many of these laboratories and access to testing for patients.

Potential negative consequences to increase regulatory requirements would include closure of some, if not many, medical center clinical genetic testing laboratories and loss of training sites for future laboratory directors, because this is where laboratory directors are trained.

And I think the FDA needs to recognize how close to the margin most of these laboratories operate. There would

be an inability to bring new tests on-line, loss of access to testing because of increased costs and scarce resources and reduction of quality of care because of less opportunity for collaboration between laboratories and clinicians, which we feel is an extremely important aspect of patient care and part of the reason why we exist in the settings we do.

It certainly isn't for the dollars per square foot that we bring into the institution. And less competition overall between laboratories. And I think we all know that situations in which only a single laboratory provides a test as a large reference laboratory. There is no way to do quality comparisons.

CLIA-certified clinical genetic testing laboratories have served our patient population well for over 20 years. We believe that our patients are best served by taking the least burdensome approach to regulatory oversight of these laboratories. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is Andrea Zachary.

DR. ZACHARY: Thanks. Good morning. I'm Andrea Zachary and I'm representing the American Society for Histocompatibility and Immunogenetics or ASHI.

ASHI is a professional association whose members are dedicated to advancing the science and application of histocompatibility and immunogenetics and promoting the highest standards of laboratory testing.

To this end, ASHI applauds the efforts of the Food and Drug Administration to improve health care through thoughtful regulatory oversight.

Histocompatibility testing utilizes multiple laboratory-developed tests, which do support optimal patient care of transplant and transfusion patients, because of the way in which the analytes are tested, the requirements for validation of these tests and the oversight of the laboratory performance.

All analytes are tested using multiple assays and technologies and often in more than one laboratory. This is necessary because of the complexity of the analytes. The reagents used in these assays are not developed within the laboratories, but by commercial companies.

These tests are high complexity as defined in the Federal Regulations implementing CLIA and require careful and expert interpretation.

Notably, histocompatibility testing is one of only two clinical laboratory sciences for which the technical supervisor

must have an appropriate earned doctoral degree.

Clinical interpretation draws on multiple sources of information, including the patient's condition, treatment, immunologic history, immunologic status and planned treatment protocol in addition to the test results.

Clinical utilization of these test results is carried out through close interaction and communication between the laboratory scientists and the clinical team providing direct patient care.

Risk to patients is reduced because the clinical care relies on multiple medical parameters. Utilization of any assay in the histocompatibility laboratory requires a vigorous validation process and undergoes careful and regular oversight.

Most laboratories performing testing for solid organ and tissue transplantation are approved by the ASHI Accreditation Program. ASHI has an elaborate set of standards that exceed the requirements specified in the Federal Regulations and, as such, ASHI is deemed by the Centers for Medicare and Medicaid Services to perform laboratory evaluations for CLIA certification.

The ASHI Accreditation Program conducts a thorough laboratory evaluation process that utilizes both an

on-site inspection and document review. Requirements for test validation include test data showing that the test meets all necessary performance criteria, description of personnel training and assessment of their competency, parallel testing with samples tested by an approved method and for methodologies new to a laboratory, blinded parallel testing with the laboratory accredited by ASHI to perform that methodology.

Further characterization of tests developed in histocompatibility laboratories is verified in international workshops and their clinical utility is established through publication in scientific and medical journals.

It is important to note that multiple government agencies and professional societies are involved in the oversight of histocompatibility laboratories. These include CMS, Joint Commission, the National Organ Procurement and Transplantation Network, the National Marrow Donor Program, the College of American Pathologists, the American Association of Blood Banks and the Health Care Facilities Accreditation Program.

Finally, we note that there are a few commercial entities providing FDA-cleared assays for histocompatibility testing.

Each year in the United States, more than 28,000 organ and 8,000 hematopoietic stem cell transplants requiring

histocompatibility testing are performed.

Most importantly, two critical tests necessary for these transplants are not available as FDA-cleared commercial products.

The first is the Donor Recipient Crossmatch, which is performed after blood transfusion by testing recipient or donor serum against target cells from the donor or recipient respectively. This test cannot be produced commercially.

The second is identification of HLA-LDS performed by DNA sequencing. At present, there are no FDA-cleared sequencing kits or automated sequencers. There are currently more than 116,000 patients on the National Transplant Waiting List including more than 91,000 awaiting kidney transplantation and 20,000 waiting for the life saving heart, liver and lung transplants.

Disapproval of laboratory-developed tests for histocompatibility testing would stop transplantation in the United States. Oversight of much needed laboratory-developed tests is a critical but daunting task.

The American Society for Histocompatibility and immunogenetics proposes that the Food and Drug Administration partner with professional societies that are already providing

needed oversight in order to permit the continued safe performance of critical laboratory-developed tests.

ASHI thanks the Food and Drug Administration for the opportunity to provide this input and is available to provide any further information that may be helpful in this evaluation process.

(Applause.)

MS. SERRANO: Our next speaker is Georgirene Vladutiu.

DR. VLADUTIU: Thank you very much. Thank you for the opportunity to speak today. My name is Georgirene Vladutiu and I am a stakeholder in the oversight of laboratory-developed tests.

Both as a laboratory professional and as president of a national organization that has varied stakeholders and that is the Society for Inherited Metabolic Disorders or the SIMD.

I am the Director of a biochemical and molecular genetics laboratory that I established 26 years ago in a hospital-based university affiliated setting. I'm board-certified in clinical biochemical genetics by the ABMG. And I want to say, at this point, that Dr. Rao just very beautifully described all of the laboratories that fall under the umbrella of the College of Medical

Genetics. It just tells you exactly what we are and what we do.

Our laboratory has specialized over the years in one particular area and that is metabolic muscle disease testing. We now provide probably the largest volume of testing in the country for this with just four clinical laboratory scientists.

The tendency of specialized clinical biochemical genetic laboratories is to specialize in certain areas, because there are so few of us around the country. We each provide a national need. We know who we are in terms of who specializes in what and we cross-refer.

I have a separate research laboratory that is NIH-funded that studies genetic susceptibility to cholesterol-lowering drug induced myopathy.

Now, the SIMD is comprised of physicians, laboratory professionals, research scientists, genetic counselors, nutritionists and nurse practitioners all invested in the diagnosis, treatment and management of patients with inborn errors of metabolism.

And though these are individually rare disorders, they are collectively not so uncommon. Biochemical genetic laboratories are required to have CLIA-certification and they participate frequently in proficiency testing programs and are

required to have quality control programs.

Most also participate in CAP-certification inspections. And I can tell you that if you think CLIA doesn't go through all of the analyte validations, CAP does. They will sit in a room with all of your books piled high and they will go through every one of them and call us in for questions.

Personnel must be accredited by state agencies, some by national level agencies, such as NAACLS for our clinical laboratory scientists. Most clinical biochemical geneticists are board-certified by the American Board of Medical Genetics, but this is not always required.

In New York State where my laboratory resides, we are required that each laboratory director has a certificate of qualification in genetic testing.

Another thing about New York State that is required that originally I was not particularly happy to have to comply with, but now I fully understand this. The Biochemical Genetics Laboratory is held responsible for assuring that referring physicians wherever they are in the country will provide for genetic counseling of their patients if we find positive results in our laboratory.

I'm glad to hear several speakers here today and

yesterday endorse the New York State Department of Health model for laboratory certification. It really works and it is forward thinking.

Most biochemical genetics laboratories are highly specialized working with complex nearly always laboratory-developed tests and often requiring invasive specimens. Most are household-based and university affiliated, but not all.

They serve a national need due to their individual levels of specialization. The market share, as you can imagine, is relatively small compared to large commercial labs, but extremely important to the patients that we serve.

While DNA and testing is included in some biochemical genetics labs, including my own, it will not replace biochemical testing due to the need for quantification of analytes.

Because of the unique properties of biochemical genetic testing, strategies to regulate laboratory-developed tests, primarily DNA-based complex tests with complex algorithms, are generally not universally appropriate for biochemical genetic testing.

We are concerned that the FDA's definition of genetic laboratory-developed testing for the purpose of this meeting includes not only lab-developed complex DNA testing, but

also our own biochemical genetic testing. And they need to be considered separately.

And I think there has been enough discussion here that that is becoming more and more apparent.

We understand the concerns of the FDA regarding the application of risk-based oversight. Diagnostic tests do play an increasing role in clinical decision making and they may not be properly validated in certain situations.

There is also something that I wanted to tell you that these concerns are taken into account in a very large part with recent guidelines developed by the Clinical Laboratory improvement Advisory Committee, CLIAC, for good laboratory practices. And you can find them at this website. There is also one for molecular genetics testing already published.

I'm going to skip through this, because I have been told to quit. And I'm sorry, I didn't realize I thought I had good time. It's important as the FDA considers a risk-based approach that the measure of risk will depend on the test setting and the tolerance of risk will depend on the testing and response to symptomatic versus pre-symptomatic purposes.

So there are so many things that need to be taken into consideration. Costs will certainly increase. Innovation

incentives will decrease.

I want to ask that the FDA, please, consider an advisory committee taking all the stakeholders into account and the Society for Inherited Metabolic Disorders respectfully requests to be included in that process. Thank you.

(Applause.)

MS. SERRANO: We are going to now skip down to Speaker 28, John Tomaszewski.

DR. TOMASZEWSKI: Good morning. I'm John Tomaszewski. I'm President-elect of the American Society for Clinical Pathology. And on behalf of the society, I want to thank you for the opportunity to speak to you.

The American Society for Clinical Pathology is a professional organization of, approximately, 130,000 members who are pathologists and laboratory professionals, many of whom perform lab-developed test in their laboratory.

I am also pleased to announce that this statement is endorsed by the Joint Commission. The Joint Commission has been evaluating an accrediting hospital laboratory services since 1979 and free-standing laboratories since 1995. Today, the Joint Commission accredits almost 2,000 organizations providing laboratory services. This represents almost 3,000 clinical

laboratories.

As a patient centered organization, ASCP's mission is to protect patient safety while promoting advances in medicine. ASCP and it's membership strongly believe that all diagnostic tests should be of the highest quality, reliability and safety and that each test should provide valid and useful information for a clinical decision making.

LDTs are an increasingly important and integrated part of standard practice for diagnosing and managing disease, predicting the risk of developing disease, informing decisions about lifestyle and behavior. They have become indispensable tools in the practice of medicine.

While LDTs represent the leading edge of clinical testing being offered to patients today, they have a solid -- and they have a solid record of advancing patient care and safety. ASCP feels that the time has come for FDA to insert its regulatory authority over high-complexity LDTs.

There must be assurances that these tests are clinically valid, performed correctly by competent laboratories and that the results are communicated to patients by clinicians adequately trained to interpret them.

ASCP supports strengthened oversight to ensure

that LDTs remain one of the key tools clinicians can use to answer increasingly complex questions regarding their patients' care.

Evaluation of LDTs, as with other diagnostic tests, should include the tests analytic and clinical validity. CLIA laboratory directors and technical supervisors are responsible for ensuring the test methods are both appropriate for the intended clinical application and provide quality results.

ASCP supports a risk-based approach to regulation through enhanced coordination between FDA and federal CLIA regulatory agencies. While high-complexity LDTs should fall under the purview of the FDA, LDTs of moderate and low complexity, those deemed to be in vitro diagnostic multi-variant assays should continue to be regulated by CLIA.

ASCP recommends an enhanced accreditation process of oversight through a combination of governmental and non-governmental organizations.

The CLIA regulatory process must ensure the data is collected and substantiates claims of clinical validity. Accrediting bodies may also have a role to play in the process. ASCP also supports the recommendations of the Secretary's Advisory Committee on Genetics, Health and Society in their May 2008 report that CLIA require proficiency testing for all non-waived

genetic laboratory tests for which PT products are available and that the Department of Health and Human Services fund studies to evaluate alternate performance assessment methods.

A balanced approach will be essential to evaluate the reproducibility of these assays with the protocol that maintains the advantages of multi-site PT, but also addresses the risks of intra-laboratory evaluation.

Clinical utility, however, remains a subjective standard depending on how clinicians utilize assay results in managing patient treatment and not on an objective quality inherent in the test method.

ASCP is concerned that requiring proof of clinical utility as a prerequisite for marketing of these assays might impede or even prevent patient access to them. The nature of these molecular assays allows for the nimble clinical intervention utilizing the latest published research.

These assays can be quickly modified to take advantage of the latest findings in rapidly advancing areas of medicine.

At this early stage, genetic diagnostic error is vital that the FDA strike the right balance. The regulatory infrastructure adopted must be sufficiently meticulous to

safeguard the public without being sober so that it impedes the emerging technologies. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is Joanne Bartkus.

DR. BARTKUS: Hi. I'm Joanne Bartkus. I'm the Director of the Public Health Laboratory in the State of Minnesota. But actually today, I'm representing the Association of Public Health Laboratories or APHL.

APHL members include representatives from state, territorial and local public health laboratories. Public health laboratories are nonprofit, publicly-funded mission-based institutions that provide data critical to informing public health actions.

These laboratories perform testing for the detection, characterization and surveillance of diseases of public health significance, including infectious diseases and also screening of newborns to detect rare and treatable conditions.

While some testing is diagnostic, must of the testing performed in public health labs is for disease surveillance and the results are not necessarily used for patient management, but rather for disease control efforts.

An example of this type of testing would have been flu-typing pre-H1N1 2009. Things may have changed since then. Another example would be the DNA fingerprinting that we do for foodborne disease outbreak detection and investigation.

Laboratory-developed tests really are critical to the mission of public health labs. Many of the LDTs used by the public health labs are what we would consider orphan tests that do not have an FDA-cleared equivalent.

Examples of these would be emerging pathogens for which FDA-cleared tests are not typically available, things like SARS, West Nile Virus, Dengue Fever, which is currently occurring in Florida, Hantavirus and a variety of other agents.

Testing for these agents in public health labs really is dependent on transfer of testing technology from the Centers for Disease Control. And many of those tests are laboratory-developed.

In addition, many diseases of public health concern in the United States are low incidence diseases or are only regionally significant.

Manufacturers are really reluctant to develop tests for these agents due to the small market size.

Measles, for example, has been eliminated in the

western hemisphere, but cases still occur in the United States mainly due to importation. There are very few commercial suppliers of measles test kits. The supply is inconsistent and sometimes of poor quality and actually manufacturers are now threatening to withdraw those tests because they are not profitable.

Even when an FDA-cleared test is available, the tests frequently have poor predictive value due to the low prevalence of many of the diseases of public health importance or because, in some cases, the test lacks adequate sensitivity and specificity, even if it is FDA-cleared.

Therefore, supplemental tests, many of them LDTs, are required for confirmation. The importance of this testing is illustrated by the fact that in 2008, confirmatory testing conducted by the New York Department of Health revealed false positive West Nile Virus results that were traced to a defective lot of an IgM ELISA kit.

As was noted yesterday, the assertion that LDTs are a disincentive for manufacturers to develop an FDA-approved test is not always the case. Minnesota has used an LDT for detection of biotinidase deficiency in newborns since 2006.

Our testing and that of other public health labs

revealed a higher incidence of disease than had been appreciated and demonstrated that there was both a need and a market for an FDA-cleared test.

Such a test is now available and is being implemented at an extra cost, but we feel the extra cost is worth it. During the time it took for that test to get to market, 39 children in Minnesota were identified as having biotinidase deficiency and were successfully treated.

In addition, the few measles tests that are commercially available are actually predicated on a CDC-developed LDT that has been used for more than 20 years. Paradoxically, now that manufacturers are threatening to withdraw commercial products, the LDT has once again become critical for surveillance.

APHL is concerned that an overly burdensome regulatory process will limit the availability of tests to meet the needs of the public health laboratory community. There is no regulatory paradigm for surveillance tests.

Our fear is that an IVD type regulatory process will lengthen the time needed for test development and implementation and will increase costs and have an adverse impact on disease surveillance.

APHL and its members are committed to quality, accurate test results are critical to public health and APHL supports rationale quality systems approach that meets the needs of public health.

When considering such an approach, we urge the FDA to consider timeliness and critical need of the test. The purpose of the test whether it be diagnostic or for surveillance, whether the test will be commercialized, the prevalence of the disease agent and the availability, quality and appropriateness of the FDA-cleared tests.

We, therefore, urge the FDA to consider the public health needs and utilization of LDTs in a public health setting and encourage public health representation on the advisory panels.

APHL welcomes the opportunity to work with the FDA on this important issue. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is Bernard Sixt from Agendia.

DR. SIXT: Thank you. Ladies and gentlemen, I would like to thank the FDA for calling this meeting and taking a significant step towards regulating LDTs.

I am the CEO of Agendia, developers of MammaPrint, which is the first IVDMIA-cleared test and the only FDA-cleared breast cancer recurrence test.

I want to address a few issues today. First and foremost, I sat here yesterday and watched many speakers talk about how the FDA oversight would stifle innovation and that patients will die as a result. We saw even pictures of tombstones and, obviously, it's natural to be scared of the unknown.

However, we have been there and survived to tell the tale. Right? So let me share our experience with you.

Back in 2005, the FDA called on companies to discuss regulating the field. Many of the industry players told us not to bother about seeking FDA-clearance. Why waste time and money getting cleared, they asked, if your competitors didn't have to do so?

Ladies and gentlemen, on the one side, I'm very proud to stand here before you and say that in the name of patient safety, we ignored those voices.

However, on the other side, it's somehow unsettling that this is such an unusual thing. Agendia's philosophy is that the industry, whether or not regulated, must always provide patients and physicians this objective proof of

technical validity of tests and clinical validity of claims.

Regulatory authorities around the globe need to play the role as independent control board is to check and confirm that we did do our job. Agendia's physicians and patients trust us to provide information for vital decisions. And they have the right to do so with the highest possible confidence.

In the spirit, Agendia submitted its data to the FDA and clearance came quickly and affordably. In fact, in the past three years, we have successfully secured four clearances around MammaPrint by simply providing all data supporting our claims.

In each case, we obtained FDA-clearance within five months. Stated simply, if you have good data, FDA-clearance is straightforward and quick. However, as clearances are mandatory in the present day, via previous authority put to rest who sat in the recent presentation, high risk tests with unknown performance are induced as it is easy to overfit data, easy to introduce bias and easy to choose incorrect validation strategies.

We agree it is incomprehensible to us that serious industrial players still insist in independent validation of widely commercialized tests.

For example, a marketed breast cancer

recurrence test predicting chemotherapy still lacks independent FDA validation. This test has already been used for clinical decision making in more than 130,000 women and surely data must exist.

In addition, the FDA oversight must also ensure clear labeling. For example, any breast cancer recurrence test properly trained and developed on tamoxifen treated tried population will mask all tamoxifen responders as low risk.

Many oncologists are surprised to learn that the label for tamoxifen treated patients only, in fact, means that the research is only valid if the patients will be 100 percent compliant to tamoxifen for the next five years.

According to no fewer than eight recent publications that's not the case. As many as 50 percent of patients are off the drug within the first four years. This lack of clear labeling seriously puts the patient at risk.

There were many to argue that FDA regulation would stifle innovation. However, with regards, specifically with regards, to commercially available clinical tests, innovation needs to be done in a very controlled manner on the QSR-designed control and it works, we are the living proof.

As mentioned, it was straightforward and quick to

clear improvements with the FDA that span technically and clinically aspects of MammaPrint.

Another aspect, very important, is that FDA, by providing a strong regulatory framework, would create a high barrier of entry attracting high quality investors. The molecule diagnostic industry has the unique opportunity to copy the biotech model and access significant funds to conduct proper research through large scientific and sophisticated trials.

Example for those are trials like MINDACT, it's a 6,000 patient trial, which is nearly completed, and ISPY-2 for which Agendia among other things provide full genome data from all patients for research and discovery to the respective research consortia.

In summary, Agendia believes that only appropriate FDA oversight and assure that medium and high risk commercially sold LDTs are technically safe and clinically effective and that stability is guaranteed by design control, while the patient safety is insured through adequate post-market surveillance.

FDA oversight would enable companies also to sustainably innovate and develop. Agendia fully supports universal and consistent FDA oversight of medium and high risk commercially sold tests. Thank you very much.

(Applause.)

MS. SERRANO: Salvatore Salamone will be our next speaker.

MR. SALAMONE: Good morning. My name is Sal Salamone. I'm CEO and co-founder of Saladax Biomedical. We started Saladax Biomedical about six years ago and it is a company that is dedicated to the development of therapeutic drug management, TDM, assays in the field of oncology.

This is an area of unmet medical need and I, as well as many others in the field, feel that TDM in this area can have significant clinical impact.

I have been in the diagnostic field for over 25 years and I have led R&D efforts that had resulted in over 70 FDA-approved assays and 200 instrument applications.

Today what I would like to do is share some of the regulatory experiences that we had at Saladax and because I believe that some of the regulation can impact product innovation.

A major impetus for starting Saladax was based on the issuance of the TDM Renaissance Committee validation guidelines for TDM assays. This was developed jointly by industry and academic representatives with a substantial input at the time

from the FDA. And these guidelines provided a de novo 510(k) pathway for the approval of new TDM assays.

So the first test that we developed was for a generic oncology drug that is widely used for a number of indication areas. And over the last 20 years, there has been a lot of publications on this drug and these publications have demonstrated that there is a great deal of pharmacokinetics variability and that by managing levels of this drug, clinical efficacy -- well, first of all, the variability can be reduced and the clinical outcomes can be improved, both in terms of efficacy and toxicity.

So while we were developing the assay, we had ongoing discussions with people from the FDA, namely CDRH and CDER. And the recommendation included in the Pre-IDE response was that Saladax should conduct a randomized Phase III prospective study, okay, to demonstrate the clinical value of our assay.

Now, in all my 25 years in the industry, I have never seen such a request of an IVD company for a TDM assay. And if you cannot imagine the impact of this regulatory physician on a diagnostic start-up company, I'll spell it out.

Following this recommendation would have shut down Saladax. The expense and time required to conduct a large

Phase III clinical trial in the same design that's for a novel therapeutic drug is prohibited for a small diagnostic company.

In a follow-up meeting with CDRH, they recognized this and, at the time, they suggested that we explore a laboratory-developed test route to make our assay available to oncologists and cancer patients.

In fact, this approach provided the only means for Saladax's continued viability.

And to further illustrate this disconnect in our regulatory process, if Saladax was able to conduct a multi-million dollar multiple year prospective study and receive FDA-approval, the CMS reimbursement for this by the technology crosswalk rule would be about $20 a test, making it really economically not feasible.

So the regulatory process for making new and innovative technologies available to Americans must be sensitive to both public health and welfare as well as to the economic realities.

A balanced and rational approach must be adopted to ensure patient safety while promoting innovation and adoption of new diagnostic tests. The prospect of extending IVD regulatory policies to LDTs will further stifle medical progress at

the expense of the American patients.

Finally, I would like to thank the FDA for putting together this meeting. I think it is a great forum for all of us to express our ideas and experiences. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is MaryDel Brady.

MS. BRADY: Good morning and thank you for this opportunity to be here today. I apologize, my slides somehow did not make it to the overhead. But my name is MaryDel Brady and I'm Chairman and CEO, CvergenX, Incorporated, which is an early-stage company that was formed in order to apply genomics to radiation therapy.

60 percent of all cancer patients are treated at least in part with radiation therapy, more than those that are treated by any single chemotherapy.

Currently, however, there are no tools in the clinical setting to accurately predict how a tumor will respond to radiation or what the optimal level of dosing should be.

Two patients then with the same diagnosis, same stage of cancer and the same treatment can and often do have entirely different results, as far apart as cure in one and

advancement of the cancer in another.

Preliminary data from CvergenX tumor-specific genomic profiling may help to determine which patients are likely to benefit from radiation therapy and at what levels of dosing. And we are currently designing our clinical trials, so I can appreciate and I hope you can appreciate the clarity in regulatory oversight is both timely and vital to CvergenX.

I am also the founding CEO of RedPath Integrated Pathology, which is another genomics-based diagnostic company, that was formed in 2004 to assist pathologists in resolving diagnostic dilemmas. I'm not here speaking on behalf of RedPath today, but I can tell you that my five years during the launch, development and growth of the company has been very formative for me on this issue.

RedPath's first test was in pancreatic cancer diagnosis and it has been successful in facilitating more accurate diagnosis of this deadly disease and equally important in saving many patients from very serious, costly and unnecessary whipple surgeries with accompanying lifelong repercussions.

Both of these companies have and are developing tools to assist clinicians with their medical decision making by providing new and more objective information and personalizing

science in ways that was unavailable in the past.

I also serve on the Steering Committee for the Coalition of 21st Century Medicine, a group of innovative diagnostic technology companies, researchers, physicians, venture capitalists and patient advocacy groups who support the development of advanced diagnostic tests that can improve the quality of healthcare for patients.

Since entering this exciting and rapidly evolving field, I have come to understand that today's diagnostics require different systems, including a new regulatory framework, which is the subject of this public forum, along with new reimbursement systems, which isn't and which aren't in the purview of the FDA, but, as you have heard from others along the way, quite frankly, I don't know how we can discuss and resolve one without the other.

With that, I applaud the FDA with the new direction that it seems to be taking and I would like to focus my remarks on a few key points that include support for the goal of risk-based, evidence-based oversight, but I encourage the FDA to reconsider a new framework that is established by notice and comment rule making.

I also support the creation of lab-developed tests and I encourage the use of NIH's Genetic Test Registry as part of

the oversight framework and I support the strengthening of CLIA and the work that it has done so successfully for so many years and urge the FDA to remain steadfast in its stated commitment to eliminate potential overlap.

What I am concerned about is the effect that new oversight policies can and to some degree already have effect upon innovation. I can tell you that the threat from firsthand basis is real. It is not imaginary. And that the continued development of new and better personalized approaches to diagnostics is closely tied to the decisions that the FDA will make regarding its regulatory policies.

Relative to risk-based and science-based regulatory policy, I believe the clear definitions and guidelines for validation are helpful to everyone, patients, clinicians, researchers, laboratories and those who are charged with oversight.

As the science of diagnosis continues to deepen and improve, the validation of that science becomes more important and often times it becomes even more measurable as it is transferred into the clinical setting. But there are a range of lab-developed tests and these ranges and their intended uses whether they are definitive or adjunctive, you know, all should be considered in determining the appropriate levels of oversight for

each.

I am fully in the camp of those who believe that diagnostics are different. They are neither devices nor are they pharmaceuticals. While recognizing that the FDA must operate under the existing device authority, I can concur with others who are urging a more flexible degree of oversight that incorporates intended use for LDTs and IVDs and reflects the science and the risks of diagnostics, not those of a manufactured device or a drug.

Clinical utility and usefulness should form the basis of the FDA's guidelines with the help from the NIH.

And finally, in regards to strengthening CLIA and eliminating overlap with the FDA that could prove to be confusing, costly and burdensome, I'm heartened by the FDA's collaboration with the NIH and I encourage and support additional collaboration with both CMS and the CDC in order to continue to expand and enhance the understanding of laboratory science to inform clinical trial design and implementation, in inform regulatory policy for advanced diagnostic tests and to avoid duplicative requirements which will impede both innovation and speed to market.

Thank you all very much for this opportunity.

(Applause.)

MS. SERRANO: Our next speaker is Gualberto

Ruano.

DR. RUANO: Good morning. I'm Gualberto Ruano. I'm the President of Genomas. I'm here representing Hartford Hospital and the Institute of Living.

I'm going to change gears a little bit, so I warn you this is going to be a case study about how LDTs have entered the mental health arena. It's not something we have discussed so far and I want to use this case study to illustrate how LDTs can influence clinical practice in an unmet medical need.

The Institute of Living is one of the most prestigious psychiatric centers in the country. It has been in business since 1822. And it has a number of centers inside the institute related to specific areas of mental health research.

We live in the Genetics Research Center which incubates genomes and the Laboratory of Personalized Health. The Laboratory of Personalized Health has been in business since 2005. It's accredited through CLIA and the Connecticut Department of Public Health.

It also has a distribution network through the Hartford Hospital Clinical Laboratory Group called Clinical Lab Partners. And this has allowed us to have reach to the entire State of Connecticut through CLP.

The clinical practice that we have established relates to mental health. The kinds of patients that get referred to us are people who have a history of treatment resistant depression or who have manifested drug intolerance side effects and some of these side effects can be metabolic side effects, such as prediabetic syndromes.

The patients therefore are already problematical. These people have had issues with health in terms of their mental health treatment. They are referred to us to figure out if there is a possible metabolic deficiency and for that purpose we do a combinatorial LDT that includes Cytochrome 2D6, 2C9 and 2C19.

Altogether, the LDT includes 34 alleles. And these alleles are then categorized according to algorithms that calculate the metabolic research of the patient and uses that to provide guidance. So I'll give you a case study of how this has been done.

We are right now being used by 20 percent of the psychiatrists in Connecticut, so that shows you that this technology has taken route in our area of service. This year alone, we are projecting 150 patients referred to us. We have exceeded the 1,000 mark already in terms of the history of the service.

One of the things that we have discovered which

is striking is most people, 50 percent of people, have alterations in two or three of these genes. The average therefore is not to be fully functional. The actual average is to have one deficiency. People who have three alterations, that's 6 percent, are the most difficult patients to treat. These people go through multiple rounds of trial and error and they eventually get referred to us, because nothing seems to work.

In fact, here is a case that we have published. This was a 54 year-old lady that went through five years of treatment with 18 psychiatric medications, not given by the same psychiatrist, by different clinicians. She was referred to us because there was a suspected metabolic deficiency and we find out that, indeed, this patient has one of the most severe deficiencies we have seen.

She had all three genes altered. 2D6 was null and she had deficiencies in 2C9 and 2C19. What do you do with a patient like that? Well, first of all you know that it has a very low metabolic reserve. She is in the lower 2 percent of the population that we have analyzed and she is part of that 6 percent that has triple deficiency.

What do you do with treatment? We provide guidance based on an algorithm that gives selection of

medications using a traffic light analogy. You see a lot of red. This algorithm has 80 brands of psychiatric medication, but there is some green and there is some yellow. So there are some options even for these difficult patients.

This patient recovered very well. She was put on one of the green medications which is Klonopin and she did very well.

I just want to also raise the point that in our field there are guidance available. These are the ones that just came out from the American Academy of Clinical Biochemistry, published in April related to pharmacogenetics. I'm one of the authors. This is available now on the website.

This work has been extensively published four years in a row being presented at the American Psychiatric Association. So the American Psychiatric Association has provided a forum for this.

So in conclusion, an LDT has been developed in mental health to meet medical needs. It has served more than 1,000 patients and we believe that this role shows how LDTs can be brought to clinical practice. And there are existing professional expertise, learned societies, peer review that allow LDTs to be brought to clinical reality to help people, which is what

we are all here for. Thank you very much.

(Applause.)

MS. SERRANO: Okay. And our last speaker for Session II is Robert Middleberg.

DR. MIDDLEBERG: Can everybody see me? Now, there is good news and bad news about being the last presenter. The bad news really for me is that there is really nothing I'm going to present that you haven't already heard, that's really bad news for me.

The really good news is I'm the last presenter for you.

So, you know, I've got to tell you, you will see the subtitle of my talk here. I'm a toxicologist by trade, so I'm going to deal with that. You know, we use chromatographic and spectrometric techniques, like LC tandem mass spec, so I feel like a little bit of a fish out of water here, quite frankly.

When I first heard the term like IVDMIA, I thought it was a new sexually transmitted disease. But with that, you know, I would like to put some things in perspective here about, does really one shoe fit all LDTs?

So first, I'll talk about the provenance of the test. You know, is it a test that is based on longstanding chemical

principles, one that it is established for many, many years. Are we talking about biological tests, biomarkers or something like that? There is a difference in my mind between them.

Is there validation provenance? And these are some documents, some as we have already heard from Dr. Salamone, that, you know, the FDA participated in. And these are for chromatographic techniques. How do you validate them?

And I have heard a lot about CLSI while I'm sitting here and, quite frankly, I sit on a CLSI committee on limits of detection. And the only reason I'm there is because I'm representing the College of American Pathologists.

90 percent of the members and participants, consultants, advisors are from manufacturers of either platforms or kits. So whether it really represents the industry as a total when they put out guidelines, I'm not so sure. And listening to what's going on, quite frankly, there is no toxicology lab in this country that can apply CLSI guidelines like LOD. It just can't happen. We will never develop a test.

So I'm not sure that CLSI is the answer. There are other agencies out there, the American Board of Forensic Toxicology, the CAP, New York State that all have processes in place to handle specific tests like these, short of CLSI.

How are the results being used? Are they quantitative or qualitative? Distinct differences between them and what should be required. Is it part of an algorithm or is it a predictor of disease state?

I fully agree as both a laboratorian and as a patient, I guess, that, yes, should there be oversight of these at a high level? I believe so, yes.

Who is running the test? Minimal competency, the IVD manufacturers, these are push button tests. None of the tests we perform are push button tests. They require training, education and a lot of experience.

So there is a difference between the IVD manufacturers and what we are doing. And who is receiving the results? Direct to consumer, other laboratories, medical professionals? Certainly direct to consumer, there has got to be some guidance there.

Other laboratories, maybe, maybe not, but medical professionals, don't shortchange these people. I deal with them every day. They use our results in light of a patient, how they are treating a patient and they put it in perspective. It's not a stand alone item.

And can the end user understand the derivation

of the results? In chromatography, it is a point in time measurement usually. It's usually understood by people and again put in perspective of what it is supposed to be.

I just thought I would show you this. This is a proficiency result from -- each line represents a different IVD. And it is for theophylline, a drug used for a number of conditions, but mainly respiratory problems, like asthma.

You can see here and all of these, I believe, are either FDA-cleared or at least the platform is and you will see ranges of results from 9 to 21. And you know, the therapeutic range is 10 to 20. So depending on where the result goes, where the sample goes, the patient is either being underdosed or overdosed, and treatment might happen anyway.

And these again, I believe a lot of them at least, already are cleared by FDA.

So sort of rounding this out, other things, what makes one LDT different than another? Quality control, we don't use equivalent quality control. We would never do that. The lab, the staff, the method, the approvals, the accreditations. I laugh at the concept that we are self regulating.

Barely a month goes by that we are not being inspected by someone. So self-regulating, I just don't get it.

And the intended use, again, appropriate regulation, I agree with completely.

My recommendation is, if the FDA is going to put something forward, it's essentially what you have heard already, stratification based on complexity, things like that. But consider deemed bodies, like CAP, like New York State, they work, it's effective, and we do it every single day. Thank you.

(Applause.)

DR. GUTIERREZ: So we're going to break for lunch now. We will have an hour lunch, so we will be back by 12:40. Is that right? Yes. We will start at 12:40 then.

(Whereupon, the above-entitled matter went off the record at 11:38 a.m. and resumed at 12:43 p.m.)

A-F-T-E-R-N-O-O-N

S-E-S-S-I-O-N

12:43 p.m.

DR. GUTIERREZ: Good afternoon. We're going to start the afternoon session. And we are starting the afternoon session with a discussion, with a table discussion here.

The moderator this afternoon is going to be Tom Hearn from the CDC. And I'm going to be nice to Tom, and instead of having him stand here for a whole hour, he is going to

sit at the table and moderate from the table. So, Tom?

DR. HEARN: Thanks very much. I thought yesterday during the session, I thought the moderator was quite good about standing up there the whole time with their panelists having their backs to her, but it went quite well. But I chose the easy way out and I'll sit here.

So good afternoon. I'm Tom Hearn. I'm the Acting Director of the National Center for Emerging and Zoonotic Infectious Diseases at the Centers for Disease Control and Prevention.

I have also been serving for quite a while as the Chief Federal Official for the CLIA Advisory Committee that we manage.

In this session, what we are going to do is follow-up on the laboratory perspective and the challenges that we talked about this morning. Thanks to all of those who provided comments not only today, but yesterday.

Let me introduce to you very quickly the panelists, and let's see if they are -- okay, I'm seeing if I have the same order here as what they are sitting in.

First, we have Dr. Karen Mann, Associate Professor of the Department of Pathology and Lab Medicine,

Director of the Molecular Genetics Fellowship Program.

And then we have Mr. Alan Mertz, who is President of the American Clinical Laboratory Association.

Then we have Dr. O'Leary, who is Deputy Chief of Research and Development Officer at the Veterans Health Administration.

Followed by Dr. Gail Vance, who is Professor of Medical and Molecular Genetics, Professor of Pathology and Lab Medicine at Indiana University.

Followed by Ms. Judy Yost, who almost needs no introduction, but to be fair and consistent, she is the Director of the Division of Laboratory Services where the CLIA Program is managed. And it's at the Centers for Medicare and Medicaid Services.

And then we have Mr. Rick Naples, who is corporate Vice President of Corporate Regulatory Affairs and Reimbursement at BD Technologies.

Thanks to all of you in advance. What we will do is, I think I'll start out and ask a few questions. I thought it worked well yesterday that at a certain point we open it up to the audience a bit.

But to kind of get things kicked off, some

redundancy is okay. I mean, I think that you need to hear how different people feel about things and how they thought about things and what their experience is. So I'm not too worried about that.

So probably as a kick off, I would open this up to all the panelists. What would you like to see with respect to the FDA's oversight of laboratory-developed tests?

You know, I think you could talk about what might be ideal, but I would be very interested in what do you think is practical? So who wants to go first? Oh, jump up and raise your hands. Dr. Mann?

DR. MANN: So I'm actually going to sort of, I think, focus my answer more as first steps we would like the FDA to take. And I'm echoing what multiple people have already said is that we really think the FDA should form an advisory committee of interested stakeholders to help them on this sort of deliberate path to judging what is the best way to oversee LDTs.

And I think it is really hard to tell what is practical and what is ideal without a lot more conversations, a lot more discussions with a lot of people. There are a lot of LDTs that are in current medical practice, not necessarily cutting edge new things, and we need to make sure that we don't impede medical

care.

MR. MERTZ: We'll just go down the line here. First of all, thank you for having us on the panel today. And the ACLA is glad to participate. First of all, I would like to echo what was just said. I think because of the complexity and the importance of this and I think we have heard clearly for the last day and a half about the value of laboratory-developed tests to the patient, we have to go forward in a very measured way.

We have to reach consensus. And to do that, we have to have the stakeholders. And what incredible stakeholders you have had, a collection of them in the last two days. I have learned a lot from them. So I think if we continue this process, I think that will be important.

I think we need to identify the gaps and fully understand them. There are a lot of elements that are important. The devil is really in the details on this. And such details, obviously, the elements is risk characterization, what evidence requirements are required.

I think it's pretty clear that we are going to need a fairly broad grandfather exception for the well-established tests that are already out there. And we have also heard a lot about having to consider the relationship to existing regulations, in

particular CLIA state regulations accreditation, New York State.

We want to make sure we avoid the cumbersome duplicative and redundant regulation.

The other point I'll make, and then I'll pass on the mic here, but we have heard this a lot, but just to reiterate, I think it is so important that we look at the actual intended use of the test and how medical providers use the information and how the result of the test will actually change direct medical treatment as opposed to, is it a serious or life threatening disease?

It's obviously important, but really when it comes to laboratory tests, it is the intended use of it and how that information is actually used, because sometimes it's just an initial screen. There are many other diagnostic tests that are going to come along, like with a pap smear, for instance, that it is not the sole determinant.

So those are just a couple of thoughts I have.

DR. O'LEARY: Defining practical is pretty difficult because it is a matter of a number of different considerations that aren't entirely obvious.

I would like to suggest a philosophical underpinning rather than a regulatory approach. I would like to first suggest that both the Agency and the pathology community

have got to recognize that there are problems with existing approaches.

Some of those problems are with the existing regulatory approach. If, for example, one asks the question is PSA safe and effective for screening for prostate cancer, at this point, clinical trials data might suggest safety is not necessarily there, even though this went through the appropriate approval processes at the time it was introduced.

So we have got to recognize that simply bringing FDA in does not necessarily provide the solution. At the same time, we have to look that the pathology community has occasionally used home brew HER2 assay in order to assess potential therapeutic responsiveness to Herceptin without a strong evidence-base.

And we are part of the problem, too, and that's why we are here. So I think that then calls upon as a community to define carefully the problems that we are going to solve and with a fair degree of precision, a I wonder is laboratory-developed tests or even high risk laboratory-developed tests sufficient precision. I'm not sure.

That we would be able to quantitate that problem a little bit, because the solution that is developed, if there is a

regulatory solution, ought to have a cost that is more or less proportionate to the problem. And if the cost dwarfs the problem, then it ends up being a poor use of health care dollars and that is a huge national consideration, even if it is not part of the regulatory mandate per se.

And then finally, that whatever regulatory approach ought to have an assessment portion built in to it to determine whether or not whatever regulatory approaches taken has actually met and addressed successfully the regulatory problem.

This is easy to say. I know it is quite hard to do. But I would suggest that as philosophical underpinnings.

DR. VANCE: Well, I would answer where the FDA should focus its interests in activities on a subset of LDTs as we have tried to outline as high risk LDTs. There are thousands of LDTs out there. Most have been offered safely and efficaciously for years.

But I would suggest that the FDA focus on that subset of tests that presents problems. I also think that the FDA should proceed cautiously. It is a difficult problem. It's going to be hard to figure out. As I said earlier, we have been working on this policy for about a year and a half now and we keep revising it

and keep revising it and taking in commentary.

I also think the FDA should proceed through comment and rule making.

And finally, whatever program is developed, it should be flexible so that those tests that might be assessed as high risk initially, that after time and methodologies understood and validation is understood and there is good clinical validity and clinical utility in the literature that those subsets then be downgraded with regulatory oversight.

MS. YOST: Good afternoon, everyone. We have had a lot of feedback already on what should happen, but from a CLIA perspective, I can see that clearly FDA needs to set a goal for what they would like to accomplish and then define the scope of how much they want to do, because this can get bigger than a bread box, I think, if you let it get out of control.

I see just from our own experience that clear and concise guidance to laboratories so that they can understand exactly what must be done and what requirements must be met.

I also still believe, I have said it for many times over, that a public and private partnership is probably a good way to go by involving all of the affected stakeholders. I wanted to echo Dr. Mertz' comment because I think that's a great way.

Sometimes it takes a little longer on the front end to develop your product, but in the longer run, you end up with a better quality.

Clearly, from our own experience, requirements have to be feasible. You have to be able to meet them and do them, but we also want to ensure the quality of the test that is being evaluated. From our perspective, we clearly offer the resources of CMS and CLIA to assist FDA in this process, whatever it is.

MR. NAPLES: Well, I certainly agree with all I heard from my esteemed colleagues up here. Flexibility, focus, and I think that I again reiterate that the solution I would like to see FDA pursue is one that embraces processes already in place; it doesn't recreate the wheel.

And recognize that for LDTs as well as for IVDs one-size-approach doesn't really fit all. What I mean by that is as we look at the LDT universe, what I have heard today is LDTs that are really for rare diseases, some of those tests are made only in a single laboratory maybe in the world for a handful of patients and I can't imagine that it would be practical to bring the full force and effect of all FDA requirements on such a test without disadvantaging patients.

There is LDTs for emerging markers, and I think

those that are out there on the cutting edge being developed by labs, I think FDA needs to regulate those with a light touch, so that they can foster and promote access to these important tests and additional test technology assessments to understand the value of these tests.

And then again, there is LDTs that we heard somebody talk about 100,000 tests a year, and that sounds an awful lot like an IVD in a high volume prevalent disease state. So I think FDA needs to have an approach that recognizes one size doesn't fit all.

DR. HEARN: Thanks. I think building on that a little bit, some of the discussion we have had so far at this meeting is talking about a risk-based approach and looking at different categories of tests.

And so I would be interested if you have ideas about how to approach a risk stratification. And related to that, I got to thinking is there sufficient evidence or data to really drive our current ability to be able to effectively institute a risk-based approach? And what are some of the factors that you might consider in that?

And one of the things that often comes up, and I want your input on it, is you think about what the risk is of

providing the test, but to be sure to think about the risk of not having a test available, which is an important part of the equation.

So anybody want to jump right in to giving us their ideas about a risk-based approach?

DR. VANCE: I have already presented to you this morning a tier-based approach to the oversight of LDTs in a low, moderate and high risk strategy. We feel that both the low and moderate risk can be adequately monitored through the CLIA Program, as they have been again for years, but we do recognize that there needs to be another component, particularly of the moderate risk category, and that would be clinical validation. And I spoke to that earlier.

Although implementation of clinical validation is not as easy and straightforward, so we had a committee that we tried to hammer out the principles of clinical validation and found that it was a circular argument in many respects.

So we have hired a consultant to go through the literature and get evidence-based principles of clinical validation. This is a responsibility in proposing this program that we feel we must undertake.

Additionally, there is the education that would come with applying these principles of clinical validation. And we

feel that it is our mandate then to educate the laboratories not only what are those principles, but how to abide by these principles in order to collect that kind of data and present it for an independent review for moderate risk.

We do acknowledge that in the inspection of the laboratory sometimes it makes more -- it takes more time to do so, though I think, you know, we have conducted fairly adequate and thorough investigations to date.

But we realize that there are some weaknesses and that if we are going to propose that there are clinical validation standards, then we must present those principles. They should be evidence-based, and there must be an education program to adapt to those.

MR. MERTZ: And this is really the most difficult issue of ACLA. We have been talking about these issues for some time with our members and our members are really the experts. They are the laboratories, and it has been a difficult thing for us.

But a couple of conclusions that we have come to is that, first of all, because as I mentioned the complexity of it, I think this is the area you are going to need the consensus the most of the stakeholders, and it may be -- there may be the need for outside panels and so forth. That's not something you could put

in a statute or you could necessarily nail down in a regulation and cast it in concrete.

But in general, again, we think that the intended use of the test is important and that really the high risk should be very limited to those where the tests might be the sole determinant or the absolute primary determinant of a serious or life-threatening disease and connected with the treatment for that.

An example for that might be HER2 testing for Herceptin or something like that. But where a test is truly adjunctive to many other tests that are going to be done, that clearly is not high and it may not even be moderate risk.

DR. HEARN: Dr. O'Leary and then Dr. Mann.

DR. O'LEARY: So I would like to echo the comment that stand-alone sort of is a particular concern, but I would suggest too that even now the stand-alones haven't really, that have gone through FDA, haven't gone through appropriate trial in that trial design that simultaneously validate the drug and the device are really required to be scientifically valid.

Such trial designs do exist. They have been published extensively in the statistical literature. They have not been widely actually applied in clinical trials, but the current

framework isn't really, at the FDA side, hasn't been absolutely adequate to addressing these issues either.

So I think this is an area that needs a lot of work on the part of the community to get it right.

DR. HEARN: Dr. Mann?

DR. MANN: Certainly AMP recognizes that there are certain tests that may require more FDA oversight and Dr. Lyon presented those earlier today. Our concern is that dividing sort of other tests between low risk and moderate risk is actually very problematic and certainly the same test in different clinical settings might be low risk versus moderate risk.

And we are just concerned that this is going to be very problematic and may not be easy to accomplish. An example, of course, would be a genetic test confirming a diagnosis in an adult of used in a prenatal setting where it potentially could lead to an abortion is a very different level of risk.

DR. HEARN: Mr. Naples?

MR. NAPLES: I think we pretty much all agree on the high risk component here that some type of FDA oversight is appropriate. I think the challenge and the opportunity is to define that moderate complexity or -- I shouldn't say moderate complexity.

See, Judy, I'm sitting next to you and I'm talking CLIA. Moderate --

MS. YOST: It's automatic.

MR. NAPLES: It's automatic. It is after many years. But it is the moderate risk test. And the example that was just given, under the CAP proposal, that would still be something that could be handled and reviewed by CAP accreditation review.

And I guess my question is if that's good enough for lab-developed moderate complexity tests, is that good enough for an IVD manufacturer moderate test, risk test? I mean, I think it's important to look at where we set the bar and how we make a determination on risk.

DR. HEARN: Anyone else want to address this question? If not, I'm going to move on. And then the panelists may have to take a note here because it's a multi-part question. It's a simple question with multiple components to it.

And I think it follows on a lot of what we are trying to get out of this entire session. It is kind of focusing on the challenges and trying to learn a little bit from your perspective about what the challenges will be to clinical labs, and if they were to have to comply with LDT Regulations.

And I think a lot of what we have discussed in the last day or so, different people have talked about different components, clinical validation which is one that most people have jumped to, but there are a lot of other components as well.

There is supply chain management of the materials that you use in developing those tests. There are design controls. There is a whole quality systems approach to development and maintenance of a test, labeling. I told you there were a lot of parts to this, so we may spend some time on this recordkeeping and reporting.

We would be here all day if we addressed every one of these and a lot of depth. I would be interested though in of these where are the labs going to be the most challenged? What needs to be done? What are your thoughts in some of those areas?

So I'm going to open it up and as long as people jump in, I won't call on people.

MR. MERTZ: Thank you. This is really the most important question, I think, and since we represent the labs and our members, I think we need to address this.

You know, I think big picture, the biggest challenge is that laboratories are laboratories. They are not

manufacturers of the products, and they were set out to design. Their whole role in life really is to provide a medical service to patients and to doctors and hospitals, and so we are traditionally regulated by CLIA.

We are a service provider, and so I think overall that is the most challenging thing and it leads to a lot of the other questions. And I'll just sort of tick them off quickly.

The inspection issue, obviously, we are already inspected by CLIA. This would be a very, you know, resource challenge. I'm sure we -- I was talking at lunch with the FDA folks, I mean, the inspections will be something that has to be considered, so we don't duplicate. Maybe some of that can be done with CLIA.

We heard a lot the last two days about how will modifications to existing tests be treated. The statement of the XDx about the AlloMap test and this is very challenging, because when does a modification require a clearance application?

Again, we are service providers. We are trying to improve tests and it might be adjusting an assay so you can increase test volumes or shifting the sequence position or primers or probes or validating additional samples. So we have -- submission to FDA at every step here would be very, very

destructive to innovation and actually the process of innovating for tests, such as was done with HIV testing back in the '90s which was so critical. As was mentioned, duplication of redundant quality systems.

And then finally, I won't get into this, but it gets also really into the challenge of reimbursement. We heard about low volume tests that Dr. Cockerill from Mayo brought up pertaining to rare diseases. When the reimbursement, infectious diseases as we heard yesterday, is so low and there is such a small volume of tests, that's going to be a real challenge of any regulatory burden.

So that's plenty to chew on.

DR. HEARN: Dr. Mann and then Dr. O'Leary.

DR. MANN: I guess I'm being called on. I mean, I agree with a lot of what was just said. You know, the things we are concerned about are burdensome and duplicated regulations and requirements. I mean, we are inspected. We have a lot of -- it seems every year we have more documentation we have to do for the tests we are doing. And that there is, you know, at least some degree of overlap in the quality measures and so on that we are required to do to do this for CLIA and CAP and some of the things FDA required.

You know, reimbursement is clearly a problem. As Dr. Caliendo said earlier, you know, clinical labs are under more pressure now than they ever have been, more financial pressure, and we don't see that getting any better in the near future.

DR. HEARN: Dr. O'Leary?

DR. O'LEARY: I think actually all that is going to be pretty difficult for the clinical labs. You know, we initiate maybe five or six clinical trials a year and maybe three of those are FDA-regulated.

I maintain a regulatory staff of about 20 individuals to deal with those and so forth and you would almost need, I think, any -- you would almost need a regulatory affairs person within your laboratory, it seems to me, to deal with the current FDA regulatory framework.

I think actually the framework is, if not outmoded and inappropriate for laboratory devices at this point, I think it will be within the next five years or thereabouts as we get into things like whole genome sequencing.

And I wonder whether or not, and this would require rule making, one needs to separate out issues associated with analytical validation of tests asserting analytical performance characteristics away from what I would call the decision making

portions of the test, the things that have to do with clinical validity.

I think it is really ripe to reexamine this framework and probably the CLIA framework together in a new way prior to going forward.

DR. VANCE: You know, I'll just tell you, this is going to be very difficult because I was standing in the Starbucks' line yesterday, as you will frequently find me, and I'm listening to biotech company representatives, consultants and IVD manufacturers and they speak a different language.

FDA-speak is foreign to laboratories. We know CLIA. We are aligned with CLIA. We go back and forth. We report to CLIA. I mean, but we don't have a clue, and I'm just speaking for myself, about FDA.

I mean, you know, QSR, Labeling, really these are terms that you guys use, or many of you, may use every day, but we don't. So there is an educational problem here. There is a chasm here that I think we have to be well-aware of and it's going to take education, education and more education to bridge that.

I would also like to reiterate what Judy already said is that we should think about a public/private partnership and utilization of third-party resources in doing this too because there are many professional organizations, including CAP that provide

education and could be the purveyors of education in this new regulatory arena, again, that most of us are unfamiliar with.

So you might consider that. You might consider deemed status, FDA-deemed status as there is something similar as CLIA-deemed status, but I would tell you that it is going to take effort and a considerable amount of effort to bridge the CLIA and the FDA worlds.

DR. HEARN: Ms. Yost?

MS. YOST: Just a couple things. I think folks have really provided some of the challenges and we probably only hit the tip of the iceberg. What I see is that this is a moving target. It's not something that is static that we can say, okay, now we know what it is, we can measure it, we can do this. It keeps changing.

I mean, it's so dynamic. Not only the types of tests, but what they are -- if they are diagnostic, whether they are only predictive, the technology continues to change for the better, which is good.

Also, in the area of rare diseases, you clearly have on the practical side for clinical validation if it's a rare disease, you are not going to really have information for patients to be able to evaluate to determine the clinical validity.

We have worked a little bit with FDA with regard to the quality systems regulations, and believe it or not, they overlap very nicely with CLIA. Again, it is probably just a matter of terminology and how it is portrayed, but the reality is, they are pretty close.

But we also don't want to create, I agree, the situation where there is duplicative oversight. That doesn't do anybody any good. Heretofore, it has actually worked quite well. We would go off and do our thing and they would go off and do theirs an then we meet in the middle when we find an LDT that we don't know what to do with. And so that works quite well right now.

I also believe that whole idea of what the use of the test is and whether it is diagnostic or predictive has to be considered. I really see a difference there. And again, the terminology and the education, I think, are key factors as well.

MR. NAPLES: Again, I agree with all that I have heard. I'll put focus on a couple of comments and I want to support them. Alan's comment about labs are not manufacturers, that's true. And I think it would be a challenge to have labs now comply with the FDA QSR if FDA moves too quickly.

But I think the way Gail described it: education,

education, education, and an approach by FDA that takes it one step at a time in implementing QSRs as they did for the diagnostics and medical device industry where FDA allowed a three year period, so that we could learn it, we could embrace it and we could improve our documentation before they start inspecting diagnostic manufacturers to that level, I think can also help.

I think perhaps the one issue I would focus on as being the greatest challenge will be clinical validation and how much data is enough. I think today that question is answered often by the old axiom, beauty is in the eye of the beholder, and I think, you know, we have differences of opinion on that, but this is where some types of standards, some guidelines in this area can really help. And I support that approach.

DR. HEARN: Thanks. I'm going to ask the next question, kind of building on something that was mentioned earlier by Mr. Mertz and that is modification of existing tests. To what extent would oversight of lab-developed tests be a problem? Because labs do tweak tests and they change them. What would be the reasonable expectations and what problems would be encountered by now having this lab-developed test oversight? Mr. Naples is ready to go.

MR. NAPLES: Could I take this one first?

DR. HEARN: Yes.

MR. NAPLES: I wanted to add my comment on that, because I think Alan is also spot on. You know, I think if I'm in the lab, and it used to be years ago, and if I had a manufacturer's test and felt that I could tweak it in a way that allowed me to have better performance for my patient population, I felt like I had the best of all worlds.

So I would hate to see FDA make a mad dash toward regulating modifications. I would rather see them focus on tests that are developed solely in-house, that there is not much literature available on and start there first, rather than going after modifications to test, because I think it's a common practice. I think the lab director is usually in a pretty good position to decide what is sufficient to demonstrate that a modification is still performing as intended.

DR. MANN: I want to make, sort of, one point which is that, you know, people are talking a lot about modifying tests. And lab directors do modify tests, but we try not to. We try to perform the same tests the same way, you know, every time to get the correct result. And really only choose to modify them if there is some compelling sort of clinical need that becomes clear that the test is not operating, you know, is not working, as we

want it.

So we really are not changing tests willy-nilly, which I know no one has accused us of, but was starting to sound like from the comments.

It, once again, would be -- you know, it all depends what the oversight is. If you had to -- you know, if it was sort of within the current regulatory framework, which I admit I don't understand. You know, I have never been involved in a 501 or a PMA submission, that could be very burdensome.

It could slow us down when new, you know, viral strains need to be identified. You know, we need to be able to change tests more rapidly, but it really depends on what the oversight entails.

MR. MERTZ: I already commented on this, but I agree with what Rick said, that it should not apply to modifications. But of course, it is important how do you define modifications. It's very difficult. But one of the things we have thought about is that, you know, unless the modification means that the test is an entirely new claim about what the intended use of the test is, you know, maybe that's a little bit different.

But if it's an improvement to the test or modification to it, we agree. And if it is an existing grandfathered

test that is well-proven, that should also not be put through an approval process.

DR. HEARN: Dr. Vance?

DR. VANCE: I want to echo what Dr. Mann just said. We try and avoid modifications because modification requires revalidation. Revalidation is another expense to the laboratory for reagents and tech time. So it's not our desire to modify. But you have to realize in the real-world, there always will be modifications and there will be modifications of FDA-approved tests. That is not our goal either.

It is very nice to have to verify instead of validate tests. It's much easier to do. So again, we don't set out to do more work than we need to.

However, in the laboratories' hands, you may not be able to follow that protocol that is established by the FDA. And I can tell you I use an AneuVysion probe set in my laboratory and it is FDA-cleared. And I have had to modify that test, because we can't get those probes to hybridize effectively on the slide, so our modification required a revalidation.

So again, you have to take real-world examples into this process as well. And I believe there always will be modified tests, not that we intend to modify tests as well.

DR. O'LEARY: And in fact, if you look at it, the fact 510(k) PMA may process don't actually provide for wide enough real-world testing to understand how things are going to work in the broad community any more than the drug approval process assures that that drug will really behave in the broader community in the way it did in the clinical trial.

The regulatory framework is narrow. The application tends to be broad, and that's true for drugs and medical devices in general. Maybe Steve Gutman had the idea spot on yesterday. He talked about transparency in this process.

And maybe that's what we need to be looking for, focusing less on that full framework, but how do we assure that the laboratory-developed test is transparent and meets some minimal standards of validation, that we use statistically valid approaches to determine sensitivity and specificity, that we avoid the use of things like discrepant analysis, which are not statistically justified, that we put confidence intervals around the claims.

That we, when we try to make a claim, that we power it using statistical power analysis, rather than drawing numbers out of our hat. I mean, there are laboratories that do this exceeding well and there are laboratories that do it badly. But maybe what we ought to be doing is leveling the playing field

for those expectations for transparency so the buyer can see exactly what they are buying.

DR. HEARN: Anybody else? One of the things that was brought up yesterday in the introductory talks by FDA is the commercially-developed test track for oversight. And then currently not a track for laboratory-developed tests.

And I guess one of the thoughts I would be interested in from you is, to what extent do these tracks need to come together or recognize that there are differences commercial companies make tests, they distribute it to a lot of laboratories, we are talking about a laboratory-developed test that, for the most part, stays within the laboratory.

Are there enough similarities to bring them together? Are the differences enough that you should be looking at them in a little bit different ways? Sure, Dr. Vance?

DR. VANCE: Well, I just want to echo what Steve Gutman said at the end of the day yesterday, that we should not be looking at business models, that we should be looking at risk stratification.

And I think that's a very important concept. I will tell you that there may be similarities through the risk stratification, but not through the business models. And I realize

there are arguments out there about that. But again, you know, when we think about LDTs from the laboratory perspective, it is a test that is developed and provided as a service to clinicians and patients, and it is not so widely spread as a test kit or an entity that we are selling to other laboratories.

DR. O'LEARY: Preanalytical considerations are very, very important. And the laboratory-developed test has a tendency to take into account the preanalytical variables that are associated with the way that they get the specimen within their own laboratory.

That degree of heterogeneity cannot be taken care of effectively by a device manufacturer unless they really, really lock in and the test is much more robust to variation and preanalytical consideration than is usually the case.

So there are, I think, some differences based on the business model. And they do pertain to risk. Though they really go into the risk stratification.

There is also a difference associated with the communication systems in place. When you buy a system, your understanding of that system is actually considerably lower than the one that you developed in the laboratory yourself.

So you are able, if you have close clinical

relationships, to convey in your discussions a lot of the concerns and the limitations of the device in a way that you may not actually be able to do it for a commercially-available system.

I don't think that speaks to superiority or inferiority of one model over the other, but it does suggest that there are differences that need to be considered when developing a regulatory framework.

DR. HEARN: Anybody else? Go ahead.

MR. MERTZ: Let me just briefly comment, that we have had this discussion with the IVD manufacturers and Rick and I talked about this for years. And we are the laboratories and, again, not the manufacturers. But I don't think it's in anyone's interest, especially the patient, if the burden is too high on the laboratory-developed test and it makes it too expensive and too rigorous to develop those tests.

That doesn't help the IVD manufacturers. It doesn't help the patients. It doesn't help us. But so what we really hope happens is that whatever regulatory paradigm that FDA uses, that it is reasonable for LDTs.

We understand that there is a reason why it has been difficult for the IVDs to come to market and maybe they do need some lessening or there needs to be more flexibility or FDA

regulation of them. And I think the labs and patients would benefit by that, too, because when I first came to this job seven years ago, I asked our laboratories, you know, would you rather buy a kit that is extremely effective with a patient or would you rather go through developing your own tests?

And they generally tell me they would rather have a kit available to be able to use that, because that's really not the business they are in of making a device. So we really would like to see the burden on the IVDs made somewhat more practical as well. It's in all of our interests.

MR. NAPLES: Thank you, Alan. And by the way, I did not pay him to say that. Just so you all know.

In fact, Alan has been very consistent in his comments. He and I have been working on these issues for about seven years from our respective standpoints. And we couldn't agree more on this.

He said very early to me, hey, Rick, we would love to have you guys make these tests for us and we said we would love to make them. But again, it goes back to Frank Cockerill's comment earlier this morning. What do you do about those low volume, low reimbursed tests?

It's very difficult for an IVD manufacturer to meet

all the requirements, do the clinical studies, get it to market for a very small $2 million market, which may then be divided up by other manufacturers if they decide to participate in it.

So I think we do really need to look at ways so that labs and manufacturers can work together to help us bring these novel diagnostics to market with the appropriate safeguards, but in a more timely manner.

DR. HEARN: What I'm going to do is I'm going to ask a question, but as I ask it, you also in the audience, why don't you think about what questions you have. I'm going to open it up to the audience after they take on this one.

And the question that I would have for you is are there any easy steps that you might start with to incrementally move the dial a little closer to where everyone would like it to be in terms of assuring quality, reliability of lab-developed tests?

Are there small steps that would be helpful?

DR. MANN: I'll go ahead. I'm not sure they are really necessarily small steps, but to reiterate part of what I said before is that, you know, I think this is the first step. You know, you have invited us here to talk, to present our perspectives. The public is here from the various perspectives and you are getting to hear that.

I think we need to -- you know, we would ask you to move on and form an advisory panel and to include these, you know, very same stakeholders, not everyone in the room, of course, but representatives of these stakeholders.

And we also -- you know, AMP is certainly willing to help and would encourage help from other professional organizations who I think would be happy to give it in trying to come up with some, at least, minimum validation standards for these lab-developed tests that we can use, because as a lab director, you know, you sometimes feel like you are reinventing the wheel.

What do I have to do? What is, you know, good enough clinical validity? And I think it would be helpful for experts to develop some sort of guidance.

DR. VANCE: I don't want to use the term easy and that's why I didn't respond, because I think everything will take effort. But I do want to comment on what I heard yesterday from the FDA as knowing the universe, mapping the universe.

And I will tell you I think the first step, in my opinion, that the FDA should do is understand the universe. And there is some accessible data already available. You have third party accreditors that know their laboratories.

CAP has all the testing menus for all the labs that they accredit. CLIA has, you know, CMS rather, similar. Not only that, we, as deemed accreditors, report our data to CLIA. So there is a resource there. There is a wealth of information for mapping the universe.

I have heard speakers talk about the genetic test registries providing this information. Well, it may supplement this information, but it won't provide all the information. Further, I think the Genetic Test Registry right now needs to define itself better as well as to what it is going to cover, because, as I have said earlier, there are thousands and thousands of LDTs out there.

And when you use the term genetic, are you using it narrowly or broadly? So I would say the first step, if I were the FDA, I would start to gather data. And there is data already available to the FDA in mapping the universe of LDTs.

And I would utilize the third-party accreditors. I would use my sister regulatory agency and start plotting that data.

DR. HEARN: Anybody else? If not, we will take questions from the audience. Line up at the microphone. Don't everybody jump up at once. Okay, sir?

MR. SALAMONE: Yes. Sal Salamone. This is just a general comment. Someone made a comment yesterday

about a parallel argument that the lack of regulations in the financial system and see what that caused and made the parallel argument about what is going on in laboratory testing.

And I don't really think that's a parallel argument. And, in fact, I find it a little damaging on many, many different levels. But I think we need to refrain from making those parallel observations.

The clinical laboratories are heavily regulated compared to the way the financial systems were being regulated. And pathologists just aren't investment bankers. And so I think as we move forward, we really should stay away from those parallels. Thank you.

DR. HEARN: Anybody on the panel that would comment? I think that was a comment by itself. Question for the panelists?

MR. WEINZIERL: Charlie Weinzierl from Children's Hospital, Boston. Just as a guideline, in the past, I have noticed that laboratories like the Children's Hospitals that create genomic type tests and use them within their community, it's quite different than Mayo Medical Labs that might do a lab-developed test and then offer it throughout the nation.

Do you see those kinds of guidelines being used

to set up where there is greater oversight of lab-developed tests so that the reference labs that are offering it in marketing and selling it nationwide versus Children's Hospital, Boston, that may sell it to Brigham and Women's and hospitals in the area?

DR. HEARN: I think another panelist may be able to tell you what is going to happen, but your thoughts about that? Dr. Vance?

DR. VANCE: That's a very good question. And it is one that we have already thought about, but haven't truly defined. And I think it needs further discussion as is taking place here.

You will remember from Dr. Harper's presentation yesterday that the LDT then was maybe a single signal test. It was done with a physician, a relationship between the attending clinician and the pathologist. It was delivered to the patient. It wasn't a geographical region. Maybe a single institution.

With that kind of practice and oversight, I think LDTs did present a lower risk than those that are developed in a credible lab and distributed across the country.

So I do think that is a consideration. I don't have an answer for you, but I think it should be discussed.

MR. MERTZ: And I'm not sure I completely understand what the policy is being suggested and maybe there is none. But one thing I think we do have to be careful of is starting to distinguish making the regulation based on where the LDT is developed, whether it is a small hospital or whether it is a small lab or a big lab.

And I'm not sure that is what you were suggesting. But I think it was said before that I think the risk should be -- if the risk-based approach, the classification, should be based on the risk of the intended use of the test, no matter where it is developed, because I don't think we can distinguish among what kind of lab develops it, because some are developed in big labs, some in little start-up labs, some in hospitals.

And I think it would be a mistake in trying to exclude certain portions of the market. If you had a bad policy, then we will have a small business exception and that will fix everything.

DR. HEARN: Okay. We will go here and then back over here.

MR. O'LEARY: Okay. Dan O'Leary Ombu Enterprises. And I'm interested in the risk classification systems that we have talked about.

So here is a somewhat simple hypothetical. If you, as a laboratory, were to buy a test from an IVD manufacturer, it would come already with a risk classification, Class I, II or III determined by the FDA.

But if you were to develop that same test in the laboratory as an LDT, it wouldn't necessarily have that risk-based classification.

So my question is what do you think in terms of risk-based classifications, in terms of the way the FDA structure has it today, and we saw some examples about what happens and then that leads to the regulatory paths, for LDTs or do LDTs need to have a totally different approach for the risk-based classification?

And anybody that feels comfortable answering.

MR. NAPLES: I think the FDA risk-based classification system has proved invaluable to clinical laboratory medicine, both for the manufacturers, for the labs and for patients.

It identifies the risks associated with a particular test intended use with higher risk tests being infectious disease, cancer diagnostics, et cetera.

And I think that it can be used for lab-developed

tests also. I don't think it needs to be changed. FDA has also integrated more flexible approach in looking at new tests that may not be high risk. And there is a de novo pathway, so that it doesn't have to go through the PMA process if it happens to be novel technology, but the test itself is not high risk.

So again, I think we should build on the principles that already exist and see if we can apply them here.

MR. NEWBERRY: My name is Bob Newberry and I represent American Medical Technologists. And we certify laboratory professionals. And I'm not speaking for AMT. I'm speaking for the 60 laboratory professionals that work in my laboratory.

And what we would like to see from all of this discussion come out of this, laboratorians, as has been said very eloquently up here, do not speak your language.

So we would like to see a standardized approach to oversight. And we would like to see it in a language that is not Harvard Law School-ese, but looks more like something that CAP, JCAHO, CLIA, AABB and all those other people that come to visit us look like. Thank you.

DR. HEARN: Any comments? That was a very valid comment.

DR. WILLIAMS: Steve Williams, SomaLogic. My question is is a hammer a high risk device? Of course, that's a fake question. If I was going to hit someone on the head with it, you would say the intended use was high risk. And if I was going to hit the wall with it, you would say it was a low risk device.

And maybe if today I'm trying to hit the nail in the wall with my hand, you might say the hammer is a very low risk device.

So my question for the panel is this, can we commit to stop talking about high and low risk tests and to start talking about high and low risk uses? And a second commitment to say that that risk assessment is relative to the best available alternative today, not absolute. I wondered if people were ready to accept those two things?

DR. HEARN: Go ahead, Dr. Mann.

DR. MANN: I mean, I would agree that, you know, judgments of risk is a moving target and it depends very much on the use of the test as I said before. And I do think, you know, whatever regulatory environment we are working under has to be flexible and has to recognize that.

DR. O'LEARY: Yes, I would actually like to take it beyond that. And I would like to consider a PSA by way of

example, because we know that PSAs are calibrated at 0 and 4, roughly. And we also know that clinicians now are looking at PSAs that might be in the 8 to 10 range and doing PSA velocities.

However, the laboratory that does that test may be actually changing the IVD between the first use and the second use. And, in fact, the laboratory to which it goes may change between the second use and the third use and so forth.

And so we have actually got a clinician-developed test that may have a significant risk associated with some form of prosthetic intervention, you know, presumably beyond that of an ordinary biopsy, which although painful is relatively low risk.

The only way to deal with those kinds of things is through disclosure at the time of reporting. And one wonders whether -- and something really good actually happened back with the ASR rule, because laboratories began to say, hey, look, this is an ASR. It hasn't been validated by FDA and you did get some transparency out of that system.

Now, I would suggest that maybe more transparency could be had by more detailed reporting and that probably isn't going to happen through a registry, because as a busy clinician, you don't have time to go look something up on the registry.

It is either going to be developed by -- sent to you through your electronic health record, if you are a place like VA, or it's going to be on your report directly if it is coming to you in private practice.

But again, I wonder whether we need a framework that goes around the question of what we tell the clinicians so that they understand what they are really getting?

DR. HEARN: I have a question here. We're going to have to wrap up in five minutes or so.

MR. GOLDSTEIN: I'm Bruce Goldstein. I work at NIH, but I'm here on my own. I have heard quite a bit of discussion about the burdens of additional regulatory oversight, but not much discussion, if any at all, on incentives.

From the drug side of things, you have got Hatch-Waxman, you have got data exclusivity for new indications and things like that.

To what extent do you think that we can create new incentive structures to encourage LDT makers to move into 510(k)?

MR. MERTZ: If I heard it right, you're talking about burdens and not the incentives and that was a great question. That's something that we touched on with the

reimbursement, but in the defense of the FDA, the FDA doesn't determine the reimbursement for the test. So that's not their charge.

But I think the government, as a whole, and really as a country, we do have to look at the value of these tests and we heard a tremendous amount in the last two days about the value of these tests.

And we are very worried about that, because without mentioning a drug or the test, I mean, on the drug side, you can have some drugs that re reimbursed in the $50,000 to $100,000 a year range and they can spend millions and millions and millions of dollars on going through a process.

But the test to determine whether that drug works or which population should be targeted to is a $350 one time test. The economics of that are 1,000 times different. That's not going to work. That's not going to work.

If these tests are going to take off and be developed and, again, it's not the charge of the FDA, but I think it is really we have to look at the reimbursement of these tests and put more value on them or else they are not going to be developed no matter what the regulation is. But the regulation is burdensome and it's even a larger problem.

DR. HEARN: Very quickly.

AUDIENCE MEMBER: Yes. I'm not sure economics actually effectively drives a lot of these things. You know, we validated in a clinical trial a drug called, or a biologic called, Zostavax, a herpes simplex, a herpes zoster vaccine a number of years ago.

It undoubtedly will reduce both pain and health care costs if utilized, although it's a relatively expensive vaccine. Nonetheless, the uptake has actually been fairly poor.

We did comparative effectiveness studies looking at coronary artery stenting versus best medical therapy. And again, we saw one month effect of the published clinical trial on utilization and then back to previous practice patterns, even though the economics was quite clear.

You know, I'm not sure that the economics really ends up being important, as important a player as we would like to say it is.

DR. HEARN: Okay. We are going to have to wrap-up. So really quickly, your question?

AUDIENCE MEMBER: Yes. I would like to go back to the case study that Dr. Ruano presented about Cytochrome P450 utilization by psychiatrists in Connecticut.

So we have a situation where there is a new LDT that has some very intriguing preliminary results. It may turn out if a Phase III clinical trial is ever done that that CYP450 test is brilliant and becomes the standard of care nationwide or it may turn out that those tests fail an efficacy standard when fully tested.

So could the panel reflect on is it good or bad using the LDT pathway? We're at the situation now where we can see this ambivalent data.

DR. HEARN: I mean, I think that was what -- I'll let one of them respond.

AUDIENCE MEMBER: How about Dr. Vance from AdvaMed, an IVD manufacturer?

MR. NAPLES: I think it would be good if the institution would proceed with publishing data and possibly going through the FDA 510(k) clearance process, so we can all see the wonderful data and patients can have access to this.

I think that we need to have these important tests see the light of day, so people can poke and prod and look at the performance data and see how good they are and decide whether to use them or not.

DR. VANCE: Can I just follow-up real quickly on

that?

DR. HEARN: Yes.

DR. VANCE: You know, there has been a lot of discussion about rare diseases and no incentives for producing rare diseases. But there is the National Institute of Health, the Office of Rare Diseases, that does provide funds.

And if you all, most of you have, have read the article in the New England Journal by Drs. Hamburg and Collins, they talk about providing research funds for bringing some of this data to fore. And I think, you know, if that gets actualized, there will be funding to do that.

DR. HEARN: Okay. Just a few seconds left.

AUDIENCE MEMBER: Just real quickly to the gentleman who is not sure about economics. There is a physician named Elaine Jeter who is the medical director for Palmetto BlueCross in Charleston. She has the Medicare Part B contract for the State of California. She is telling all the labs in California that she is the arbiter of which tests will be on the market or not, what they will be paid and that she is the determiner of what clinical utility is for these tests.

So the pointy end of CMS' policies being executed by a contract medical director in South Carolina, that's actually

having more power in influencing my space than the FDA.

So you, I know, aren't the CMS, that's a different body, but it is in HHS. Taxpayers will not understand why CMS and FDA cannot coordinate on this kind of policy, because you are both part of the same department with a similar fundamental large mission.

So I think that's something that has to be addressed. Economics will have a huge effect on this and any other understanding is not grounded in reality.

DR. HEARN: Okay. Any comment?

(Applause.)

DR. HEARN: Okay. Last question.

AUDIENCE MEMBER: So I would like to ask the group to comment on the flexibility of the system going forward. Dr. O'Leary mentioned the fact that maybe we should be looking at a fundamentally new system that takes into account analytical validity as a separate framework from a decision making framework.

And I think this is going to be really important as we go forward, especially as we look at -- I know that they cytogenetics folks were here last week talking to you about array-based diagnostics in the cytogenetics world. And treating

cytogenetic arrays as imaging type instruments where there is an analytical component and then there is a decision making component and those are two very, very different things, TC and the PC component.

And I think that we are faced with many of the same issues going forward in the DNA sequencing world as we begin to think about NexGen sequencing of whole genomes. I'm thinking particularly hematological malignancies and subsequently we will be seeing this in solid tumors.

And the present system is not going to work incredibly well in that context. And I would really be curious to hear what the Committee has to say about that.

DR. HEARN: Any of the panelists want to? Sure. Dr. Vance?

DR. VANCE: I'll just say that I agree with you. And I have colleagues that were here last week, I wasn't, but this is secondhand information, so if it's inaccurate I apologize. But that there was some understanding and acceptance by the FDA that there were two different components and they would look at them separately.

DR. O'LEARY: I guess just to put it out in this form. In many ways, the broad platforms, whether they be large

chips or DNA sequences or whatever are getting to be more reminiscent in many ways of radiology devices than they are of the traditional single analyte LDTs.

And certainly the radiology devices pose their own challenges, but it may be that in a sense something that is closer to engineering considerations becomes very important in understanding these very complex kinds of devices, whether they be submitted by a laboratory or they be submitted by industry.

And it seems to me that the separation of clinical utilization from analytical performance characteristics is almost inevitably going to be driven by the nature of these devices. The way they are brought into medical decision support systems in the future, I just can't see how the traditional framework can work over the long haul.

DR. HEARN: Thank you. I would like to thank all the panelists for their contributions today.

(Applause.)

DR. GUTIERREZ: So we will take a 15 minute break now and come back.

(Whereupon, at the above-entitled matter went off the record at 1:51 p.m. and resumed at 2:04 p.m.)

DR. GUTIERREZ: We're going to start with the

third session of the afternoon. And we are going to begin with the public comments under direct consumer session.

MS. SERRANO: Thank you. Our first speaker this third session is going to be Anne Wojcicki.

MS. WOJCICKI: Okay. Thank you for inviting me here today. Before I go through actually the whole presentation, I want to really make four points critical to this Committee and to everyone here about why 23andMe was started and principles that are core to our values.

First, we are a company of individuals who are passionate about educating individuals about genetics. We update our blog daily and we have over 13,000 regular readers of our blog.

Our Genetics 101 video has had over 140,000 views on YouTube alone. We also have over 80,000 users who have signed up for demo accounts.

Second, we also believe that there is a significant untapped potential for the entire health care world to engage consumers in research and in their own health. We believe it is time that consumers are seen more as partners in health rather than subjects.

Third, we passionately believe that information --

that individuals have the right to get access to their genetic information. 23andMe is committed to working with the FDA to make sure that individuals continue to have that right.

Last, we believe that the opportunity for preventative medicine is here and now. Knowing my genetic profile could be a significant part of helping me prevent disease.

So we started 23andMe with a very holistic approach to genetics. We wanted people to be able to learn about scientific research and ancestry through their genetic information. We did not want to do one area or another, but we wanted to have a holistic approach.

One of the most important things that we have learned is that people are discovering information about themselves that they did not already know. It could be that they are a carrier for Alpha-1 antitrypsin or that they are higher risk for a blood clotting event.

If I look at any of you and I make judgments about your background, I could be making faulty assumptions. Could you be a carrier for sickle cell? Could you be a carrier for BRCA1 and 2? Medicine needs to move from making background assumptions about individuals and embrace molecular medicine.

We strive to present information to our

customers in an easy to understand format. Based on feedback from our customers and from usability studies we have conducted, we have confidence that customers are understanding how we present the data.

We are quick to make changes to the site when we learn that there is any confusion. Our site is updated weekly and we are constantly trying to improve.

A big part of being direct to consumer is pointing individuals to external resources to get help or to learn more. We have pages like this throughout our site that point people to their physician or to genetic counselors.

A unique and significant part of our site is the research component. If you look at communities like Livestrong and Susan G. Komen, there is clearly a significant interest in individuals to contribute to disease research in a meaningful way. We give individuals that platform for contributing to research.

In 2009, we launched our first disease community in Parkinson's Disease. We enrolled over 2,000 individuals in the first three weeks alone. We have over 4,000 participants today.

This is a very active community where over 75 percent of the participants have taken at least the Parkinson's survey alone.

We hear on a daily basis from customers through our community or through our customer service departments that people appreciate the value of the community. We think that the community is a very important part of our site.

Last month, we published our first paper based on our community findings. Our goal is to continue to publish our findings as well as to give our customers a sense of pride about the research they have helped create. We are creating electronic badges for customers who have participated and are talking about giving microattribution to all customers who want to be associated with the paper.

We want our customers to feel like research participants and not research subjects.

Our research program is set up so that we are running hundreds of Genome-Wide Association Studies on a nightly basis. We have been able to replicate many of the major genetic findings and plan to publish more soon.

We think that this database could be extremely helpful for quickly advancing genetic knowledge. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is Adele Schneider.

DR. SCHNEIDER: Good afternoon. My name is Adele Schneider and I'm a clinical geneticist and the Medical Director of the Victor Center for Jewish Genetic Diseases at Albert Einstein Medical Center in Philadelphia, a nonprofit organization that promotes education, genetic counseling is screening for up to 18 genetic disorders that occur with a higher frequency in the Ashkenazi Jewish population.

Our goal is to screen young adults prior to marriage and pregnancy, so that they may have the greatest number of options to have children free of these preventable diseases.

As a practicing clinical geneticist, I seek to ensure that tests are accurate and the test results are appropriately interpreted and communicated to patients in a manner that ensures patient comprehension of the results and their implications.

Too often have I been at the other end of phone calls from a patient whose primary care provider ordered genetic testing without providing genetic counseling and have had to pick up the pieces under emergent conditions, explaining to a distressed person what their results might mean.

I'm concerned that companies offering direct to

consumer testing are not necessarily obligated to obtain informed consent from customers or to include an appropriately trained medical professional with testing process.

As a result, individuals who are tested, may not understand the test results, may take no action where one would be beneficial and fail to take steps to prevent a problem. This might be a missed opportunity to provide good preventive care if the interaction bypasses the person's medical provider.

Some direct to consumer companies test for BRCA1 and 2 mutations that occur at a greater frequency in the Ashkenazi Jewish population without counseling or adequate and meaningful informed consent.

It is also possible for a minor to order testing from these on-line companies. Since the first principle of medical care is to do no harm, these practices would seem to be counter to the medical model of helping patients and not doing anything that might cause unnecessary distress or harm.

Laboratories offering direct to consumer testing may expose the public to harm in several ways. First, the failure to provide adequate guidance in test selection and proper counseling about the benefits and limitations of test results may lead to lack of recommended medical care or unnecessary medical

care that would have been avoided if genetic counseling was part of the process.

Test results provided by direct to consumer companies are often not offered in a format that the average individual can understand, as was noted in an article in the May 2010 issue of Genetics and Medicine.

Many do not provide a health professional to explain these results. Regulation is needed to ensure that the tests are reliable and clearly explained and results provided with the help of a medical professional.

Second, there are few laws that require direct to consumer companies to protect the privacy or confidentiality of consumer information. And some companies require consumers to consent to the research use of their samples as a condition of testing.

When IRBs approve a study using DNA, it has to be clear what is done with the remainder of the sample. Similar consumer protections should be provided by labs offering DNA testing.

Third, the clinical utility of many of the tests on the direct consumer panels has not been established. Some panels have large numbers of tests with detection rates below 10

percent. That is not really a useful test, but makes for good advertising as in we screen for over 100 disorders.

But this is not truth in advertising and is misleading the public. I would ask that regulatory agencies and perhaps the National Medical Organizations clarify what detection rate constitutes a valid test.

So tests in these panels actually provide useful information for the person being tested.

Finally, direct to consumer companies fail to disclose clear conflicts of interest, such as the use of paid advisors as spokespeople without disclosing their financial relationships to the company on the website.

As the medical director of a Jewish Genetic Disease Screening Program, I have a specific concern relating to Tay-Sachs disease. Since the Hex A enzyme assay became available in the 1970s, over one million people have been screened for Tay-Sachs and the incidents of the disease in the Ashkenazi Jewish population has fallen by 90 percent.

The optimal screen for Tay-Sachs disease is enzyme assay with a DNA test and this has a 98 percent sensitivity. The enzyme assay is done on blood. Direct to consumer companies are testing DNA only on salvia.

In a recent article that we published in the American Journal of Medical Genetics if you admit the enzyme assay, you will miss 11.4 percent of Ashkenazi Jewish carriers, since it is no longer a homogeneous population.

My fear is that members of the public believing that they are obtaining good medical care will be tested by one of these direct to consumer panels and will not know that they are, in fact, Tay-Sachs carriers and soon there will be babies born again with Tay-Sachs disease. Thank you for the opportunity to address this meeting. Thank you.

(Applause.)

MS. SERRANO: We're going to actually skip to the fourth speaker, Jeremy Gruber.

MR. GRUBER: My name is Jeremy Gruber. I'm the President of the Council for Responsible Genetics. CRG is a public policy organization that represents the public interest and fosters public debate about the social, ethical and environmental implications of genetic technologies.

We appreciate the opportunity to comment on direct to consumer genetic testing. Our current concerns with the industry and our firm belief that responsible oversight of the industry is necessary. Additional detail may be found in our

submitted materials.

While genetic testing has grown as a medical practice over the past decade, the range of gene variations tested for clinically remains narrow. This is due to many reasons, including the cost of testing and physician's ability to rely on other indicia of the disease risk.

Primarily, however, physicians have been reluctant to delve into genetic testing prior to the robust development of scientific knowledge and understanding over the relationships between genes, human health, human environment and lifestyle.

Despite such reluctance on the part of health care providers to order and interpret genetic tests, private firms have begun to offer these testing services directly to the consumer. These companies offer individuals the opportunity to discover if their genomes possess SNPs associated with disease in cancer risk, nutrient metabolism and drug response metabolism among others.

They further offer risk assessment services which look at several genes simultaneously to get probabilities of disease development over one's lifetime and offer diet and lifestyle recommendations on the basis of these genetic test results.

Some of these associations and interpretations, however, are based on incomplete and inconclusive scientific evidence from which direct to consumer genetic testing companies extrapolate conclusions.

Furthermore, the scientific basis for test results, interpretation and risk calculation remain trade secrets and are, therefore, not disclosed to consumers. Beyond such questions regarding the clinical validity of direct to consumer genetic tests then, the analytical validity, the accuracy of the genetic test for SNP variations is also largely unknown to consumers and regulators.

Nevertheless, the risk posed to consumers by faulty information remains very high. Consumers may make drastic prophylactic decisions when faced with high cancer risk, for example, or dismiss important preventative and screening recommendations in light of information they are at low genetic risk.

Where the link between genetics and risk is dubious, these decisions may be medically dangerous. Furthermore, consumers may rely on information regarding drug tolerance metabolism in deciding how to medicate existing diseases, important medical decisions that should be made on the

basis of scientifically sound information.

Finally, the information provided to consumers, both regarding genetic risk and information regarding familial genetic relationships can have significant psychological and emotional impacts.

We urge the FDA to request that data demonstrating the clinical and analytical validity of all these genetic tests in the analytical tools, including algorithms or software programs that calculate disease risk based on several SNPs be submitted to ensure accuracy.

CRG also urges the FDA to require disclosures regarding the scientific evidence behind health and lifestyle recommendations given to consumers on the basis of these genetic test results.

Furthermore, we believe direct to consumer genetic firms should be mandated to disclose the accuracy sensitivity and predictability of any results to consumers as well as potential psychological, personal and health risks associated with inaccurate results and uncertain clinical validity.

Additionally, the Council for Responsible Genetics has significant privacy concerns with purchasing genetic testing services in an online commercial marketplace as consumers may

turn over their DNA and other personally identifiable information to companies without a clear understanding of the privacy risks and without clear guidance as to their legal and regulatory rights in this area.

While the FDA may not have full oversight over all these issues, we believe these issues must be fully aired in any discussion of the direct to consumer genetic testing industry and that the FDA, FTC and other agencies work together to comprehensively address those privacy concerns within their purview.

There are currently no clear guidelines on the ownership of genetic material and the information derived from it nor are there clear guidelines with respect to protection of customer privacy by the direct to consumer genetic testing industry.

Indeed, consent forms and privacy policy is very widely within the industry and without standards can be unclear and often subject to change.

Whenever identifiable DNA samples are collected and stored, there is a high risk that violations of genetic privacy will follow. The methodology by which the information is secured is essential, yet without standards and oversight, we still

know very little beyond the assurances of the industry as to what specific controls are used.

Moreover, the privacy policies of direct to consumer genetic testing companies are not subject to health privacy regulations issued pursuant to HIPAA and there are few state and federal privacy rules that apply.

It is essential that personal information should be protected by security safeguards appropriate to the sensitivity of the information.

Additionally, there is no transparency as to the degree to which personally identifiable health information is de-identified, because not all de-identification techniques adequately anonymize data. It is important that the process employed by the industry is robust, scalable, transparent and shown to provably prevent the identification of customer information.

Finally, many DTC companies have adopted financial and data sharing relationships with third-parties as part of their business model without sufficiently explaining to customers the extent to which this may occur and the potential negative consequences without asking for specific consent for these purposes.

An affirmative written request must be required before DTC companies can use any customer generated information in this way. We urge a complete review of all policies and practices to ensure customer privacy is adequately respected, that full oversight is guaranteed.

CRG is glad to offer any assistance it can provide as this process continues to unfold. Thank you.

(Applause.)

MS. SERRANO: Katherine Borges is our next speaker.

MS. BORGES: Good afternoon. My name is Katherine Borges and I am the Director of ISOGG, the International Society of Genetic Genealogy. ISOGG is a nonprofit organization of over 7,000 members spread throughout the United States and in over 60 countries.

Our mission is to promote and educate members and the general public about the use of DNA testing for genealogical and ancestry purposes. We are comprised of serious enthusiasts who represent an active core of the estimated one million people who have taken DTC tests for genealogy and ancestry purposes since their inception, approximately, ten years ago.

As the name of our society implies, our focus is primarily upon using DTC tests for genealogy. But a growing segment of our membership also uses personal genome tests to trace health-related information within their families.

However, testing for ancestry and anthropology is far and away the largest segment of the DTC genetic testing market. This clearly does not fall under FDA's area of responsibility. Our concern is that FDA should not attempt to expand its regulatory authority beyond its proper domain of medical applications and it should assure that its actions in the medical area to not inadvertently impact the non-medical applications.

ISOGG is a dues-free society with no funding sources. The organization has no direct financial stake in any proposed regulation and is not affiliated with or financially supported by the companies offering these tests.

However, our members understand that they would bear the impact and resulting costs of any regulatory matrix imposed upon testing companies. First, is taxpayers and secondarily as consumers of the services they offer.

Our membership is not opposed to regulation that works to protect or help consumers where a clear need for

legislation is evident and an agreed upon national purpose is fulfilled.

In 2008, we supported GINA and many of our members wrote to their legislators to urge them to pass this important bill. Additionally, in 2008, ISOGG encouraged and facilitated the development of Y-chromosome nomenclature standards for short tandem repeats or STRs by the National Institutes of Standards and Technology and their subsequent adoption by all of the ancestral DNA companies and labs.

These standards were published in the fall edition of the Free Access On-Line Journal of Genetic Genealogy. This initiative for voluntary standards by a private organization is similar to the implementation of voluntary standards such as those of UL and NEMA in the electrical industry and ANSI standards in many others.

The great majority of our ISOGG membership feels strongly that any expansion of FDA regulatory authority that would have the effect of preventing consumers from ordering DTC tests would be unwise and unnecessary.

At a minimum, no action of that sort should be taken without credible, compelling, scientific data to support such a move. Relevant studies of this nature and quality are currently

being conducted.

In making these statements, I have in mind the role of the media and certain written academic opinions that over the past few years have sought to impact this issue.

Sensationalistic media articles that relate anecdotal cases should not be used as a basis to regulate. Many of the articles I read have been biased reflecting the authors views without presenting voices from both sides of the issue.

For example, just last week, a D.C. area reporter was looking for stories from consumers of DTC testing for an article to be published in anticipation of this meeting. He was contacted by several individuals who have positive testing experiences, but he did not follow-up on these contacts.

He told another consumer that he was specifically seeking negative experiences. Even more seriously, we see a tendency towards a paternalistic attitude by certain groups in the medical professions who seek to limit access to medical information that is not directly under their control.

Their arguments often express an extremely low opinion of the ability of people outside of their own professions to comprehend any genetic information or to come to terms with implications. Yet, we heard Colonel Magill of Walter Reed state

here yesterday that sometime he sees a patient who knows more about a medical issue than he does just from personal research.

A mandated intermediary would impose yet another cost to consumers. Additionally, over regulation can even negatively impact participation in scientific studies. My own mother signed up to participate in Kaiser Permanente's genome study, but then she backed out for the very reason that the results would not be returned to her.

A barrier to access to one's own genetic information seems contrary to the intent of HIPAA Law and to the new rules issued last week by the White House requiring health insurance companies to provide free coverage for screenings of laboratory tests and other preventative care.

The general view of ISOGG's members is that regulatory agencies should not stand between a consumer who wishes to collect data on their own genome and labs that can provide that service.

The genome of an individual consists fundamentally of information and every individual in a free society.

(Applause.)

MS. SERRANO: Sorry, I knew it was going to

happen at some point. Before I go on to the next person, we do have a phone. We think it belongs to Tim O'Leary. If he wouldn't mind just waiving his hand to me and I will return it. Anyone? Okay. We will find him later then.

All right. Our next speaker then is Destry Sulkes.

DR. SULKES: Hello. My disclaimer is that the views and statements expressed by me are provided for informational purposes and do not necessarily reflect those of my company Medivo nor the Alliance for Continuing Medical Education nor their representatives.

Okay. So my name is Destry Sulkes. I'm a physician and a co-founder of Medivo, Incorporated. And I'm also a volunteer board director and the treasurer-elect of the nonprofit 501(c)(3) Alliance for Continuing Medical Education.

I'm here to discuss the LDT issues surrounding direct to consumer DTC health care practices and specifically how they relate to genetic lab testing and physician oversight.

My statements are based on my daily interactions with health care providers and with patients as a physician and as a principal of Medivo.

Since 2001, our company has provided virtual health care services when and where they are needed. And one

such service is providing independent physician oversight for a variety of organizations that receive lab test requests from individuals on-line.

This oversight is conducted safely and securely by our nationwide network of credential positions on the telephone, via telephonic access, and over an on-line platform.

In addition, as a result of the rapid growth of the laboratory-developed tests in genetic lab testing over the past few years, we rely on publicly funded medical education programs from the CDC and NIH to identify an increase to the genetics communication competencies for our physicians.

I would like to provide some clarity on terms that have been used widely and we think unfortunately interchangeably in this industry.

The term direct to consumer itself was used in 1997 by the FDA to describe a method of advertising that provides valuable product information and increases consumer awareness and not for consumers to bypass their physician and directly obtain a prescription medication.

In contrast, the term direct access testing describes a different process where some states have allowed individuals to order a limited set of the safest and most well

established lab tests without a request nor the requirement for a physician's order.

The equivalent term in the pharmaceutical industry is over-the-counter or OTC, where a consumer can, in fact, directly purchase a drug in a retail setting with no physician oversight.

The confusion has arisen where DTC when used to describe genetic lab testing has come to mean that individuals may order their own tests, despite the fact that this category of lab tests are still largely in a research stage of development with the most challenging results to understand.

Interpretation of the reports is difficult even for physicians with knowledge of the patient's full history and health context. And given the breadth to the associations under study, research on their overall impact on health outcomes is inclusive.

So this is why we maintain that physician oversight is essential to safe and effective communication of genetic lab test results.

While the genetic testing industry has well established protocols and standards mentioned here earlier today and yesterday for genetic testing results as developed by the Medical Genetics Sub-Specialty of Internal Medicine, they focus

largely on inborn errors of metabolism, hemoglobinopathies, chromosome abnormalities and neural tube defects and, of course, a handful of drug response tests.

But of course, the majority of the new LDTs lack such standards. So given the variability and the categories of genetic tests, the present proliferation of organizations who offer these tests, the significant challenges for the test interpretation and ultimate uncertainty around the impact of the test results on patient health, independent physician oversight is instrumental and vitally important to protect public safety.

I want to share the impact of what we are talking about today from the view of a family physician colleague. One of her patients, a 25 year-old woman, got her genome tested for her birthday. Her intent was to use the information mainly for entertainment to share with her girlfriends, but also to see if she had any risks for inherited disorders that she could pass on to her children.

The results come back and luckily she has low genetic risks for many illnesses, but she did have a high risk for venous thromboembolism. This scared her. She was immediately thinking should she stop taking some medications? Should she start taking something prophylactically? So she called

her doctor.

Her doctor immediately did what doctors do, immediately reviewing family medical histories, hearing that she has recently taken two cross-country flights with no ill effects, considered it all and counseled her that she was most likely in no immediate risk and probably did not need to be on a medication immediately.

But with the new risk information, she would be sure to include that in her future ongoing care.

So in summary, these genetic tests and LDTs have the potential to deliver tremendous health care value over time and continued access to them is an important goal. With the help of everyone here, we can create a solution that maintains and broadens the benefits to all of us and our families in the future.

I would like to extend my thanks to the FDA for allowing me this time to present these views on this important topic. Thank you.

(Applause.)

MS. SERRANO: While I'm pulling up the next slide, we do have the cell phone if anyone is missing it. It's a black flip phone Motorola, just come find me. I'm in the front.

Our next speaker is David Becker.

DR. BECKER: Hello. My name is David Becker. I'm Chief Scientific officer of Pathway Genomics. We are a small genetic testing company with a CLIA-certified lab in San Diego, California.

Thank you to the FDA for allowing us to comment today.

There are benefits and risks to an application of genetic information and all of the companies must insure that testing provides accurate and reliable genetic information and that it's responsibly reported.

We share the responsibility with the FDA to protect the public. Protection occurs at many levels: Analytical validity, responsible translation of the information, explanation of the possible benefits and limitations that genetic information can provide, physician and genetic counselor involvements in delivering the data, such as direct access testing, it was just mentioned.

While this is not the traditional doctor/patient relationship, it does provide the opportunity for trained experts to review and explain the results and will facilitate the use of genetic information.

Proper support and education is key in this

process. This information informs better health care, but it is also just one piece of the puzzle. It can encourage personal engagement in health decisions, which is definitely the theme in medicine today. And it can also facilitate proactive prevention leading to better personalized care and lower cost.

The types of genetic reports that are delivered have a broad range. And the possible risk is relative to how the information is used. Shown here at the bottom from left to right of low risk at ancestry, wellness and motivation factors that are non-diagnostic risk information, all the way up to autosomal dominance and treatment choices.

While the slope and shape of these lines can be debated, we all agree that different tests carry different risks. Some of the risks can be mitigated through education and further reduced through the use and involvement of physicians and genetic counselors.

Any new regulations must be flexible and very responsive enough to it to adapt to the current culture as well as future innovation.

We feel that the regulatory infrastructure is mostly in place today. Shown here is the landscape from no regulation over ancestry tests that is currently in place all the way

up to FDA regulation of commercial devices and the gap that we are all discussing today.

That gap is partially filled by the new regulations or the recent updates to the CAP checklist, plus including enrollment in the Genetic Test Registry.

We think that there still may be some need for further improvements in both of these, but this is a start for today.

We encourage FDA to continue to use enforcement discretion while requiring CAP accreditation and mandatory enrollment in the Genetic Test Registry.

We feel this will increase visibility into the variety of genetic testing services and transparency on testing protocols. This will provide/allow the provision of information about the genetic tests and will allow review of performance metrics and claims around the tests.

Implementing this will currently allow FDA time to collect data on the potential risks and the proper improvements that need to be made to regulation.

Existing regulatory structure ensures accuracy of the testing, proficiency standards, validation standards, rigorous quality management, transparency of testing services and methodology.

These provide the framework for a risk-based regulation and improvements to these systems is all that may be currently required.

In conclusion, Pathway respects the need to protect the public and provide reliable genetic information and we all share in that responsibility. Genetic reports are not all equal and come in various levels with various types of oversight necessary.

Existing regulatory infrastructure provides a strong solution, proficiency and accuracy, rigorous quality assurance, transparency and testing and requiring CAP and accreditation and enrollment in the Genetic Test Registry could provide and meet the needs for oversight that can promote innovation in a rapidly changing environment while protecting the public.

Again, we appreciate the opportunity to present today and look forward to continuing our work with FDA to find practical solutions to this regulatory challenge. Thank you.

(Applause.)

MS. SERRANO: Our next speaker is Amy DuRoss.

MS. DuROSS: Good afternoon. Thank you for including me in the presenter list. It's a real honor to be here

today. My name is Amy DuRoss. I'm the Vice President of Policy and Business Affairs at Navigenics. I am briefly going to introduce our company to you today.

The company's mission is to combine advances in genomics and technology to improve health outcomes across the population by providing clinically actionable genetic insights to motivate behavior change.

We are based in Foster City, California and have been in operation for over three years. We are very proud to be licensed in all 50 states, including the State of New York and our product is called the Navigenics Healthcompass, which analyzes markers for 28 conditions and 12 drug gene interactions with genetic counseling support throughout.

You are no doubt used to seeing these kinds of statistics around noncompliance, the problem as stated by the Father of Medicine, Hippocrates, that has plagued humanity since ancient Greece.

As mentioned on the prior slide, triggering positive behavior change is the goal of our service and our aim is to reverse these trends in favor of proactive engagement for better health.

Okay. Our service is simple. It's a five step

process. First, we accept a saliva sample at our CLIA lab facility in West Sacramento, California where we convert raw genomic data to genetic risk scores available through an on-line secure web portal.

Step 5 is a series of scientific and clinical updates as new information is validated. And undergirding the whole process from start to finish, even before purchase decision is made on behalf of a patient is genetic counseling support 24/7.

Our service contributes to clinical utility in three major ways. Really primary prevention first, detection and diagnostic aid second and drug sensitivity third.

We believe there is an important and central role for health care professionals to play throughout the process, in addition to our own genetic counseling service we have in place, educational webinars for personal physicians. Patients can order the test through their doctor and personal physicians can speak to our genetic counselors for free at any time to review their patients' results.

Each of our genetic counselors is board-certified by the American Board of Genetic Counseling and has received extensive specialty training and personal genomic counseling.

All individuals who are interested in testing or

whoever received genetic results through Navigenics have access to these genetics experts to address questions and enable informed decision making.

Our members personal physicians have unlimited access to our staff, as I mentioned. It is also worth noting that these professionals adhere to a rigorous set of bioethical standards and receive no incentives to guide individuals to test when it may not be appropriate.

Every individual who chooses to test with Navigenics is personally contacted to schedule genetic counseling consultation to discuss the results, identify resources and facilitate dialogue with their own health care providers.

The majority choose to engage in this service and report feeling better informed and empowered by the interaction.

We are delighted to work with some of the leading clinical research partners and Fortune 500 employers devoted to prevention in the country. We have been proactively engaged with FDA and other agencies in Washington as well as at the state level since before launching our Healthcompass Service in 2008.

We are here today in that same spirit of cooperation and are eager to participate in development of a

balanced and science-based regulatory pathway forward. Thank you for the opportunity to speak today.

(Applause.)

MS. SERRANO: Kenneth Emancipator is our next speaker.

DR. EMANCIPATOR: My name is Kenneth Emancipator and I am an officer and executive committee member of the American Society for Clinical Pathology. I am also a pathologist who spent many years in both industry and the clinical setting.

Direct to consumer testing particularly as it relates to genetic testing is an area of growing concern to ASCP. ASCP is a patient-centered organization committed to optimizing patient health outcomes.

In order to ensure optimal health outcomes, patients choosing tests marketed and sold in direct to consumer commercial transactions should review results with their physicians and utilize CLIA-certified laboratories.

ASCP believes that the appropriate regulatory framework for DTC testing must simultaneously protect patient health while fostering an environment that encourages the innovation of more advanced testing technology.

All testing devices regardless of their level of complexity or of the qualifications of persons performing the test should be reviewed before their use on or by patients.

Moreover, claims of clinical validity for each device should be conducted in an environment similar to that for which the device is intended.

Traditionally, physicians have been responsible for ordering tests on their patients. DTC genetic testing, however, presents a new paradigm. The rapid evolution in genetic testing technology coupled with the emergence of personal genome testing companies has created increasing opportunity for patients to be more involved and to make more decisions about their own health care.

This has the potential to be both good and bad. Proponents of DTC testing argue that it provides patients risk assessment information that allows them to proactively search for specific genetic variants of interest.

However, ASCP believes that it also presents a myriad of issues not only for patients, but also for clinical laboratories, physicians and insurance companies. These issues include, but are not limited to, the ability of patients to understand test results, various validity issues, legal and liability issues.

Perhaps most worrisome is that DTC testing will generate undue stress and the worried well, individuals who over-interpret their test results.

Therefore, ASCP recommends that laboratories performing such tests provide patients easy to comprehend test results. For optimum patient health outcomes, patients should consult with their physicians for proper interpretation of those test results.

Currently, the clinical value, if any, of most DTC genetic tests remains unproven. The presence of a particular genetic genomic variant in a given individual, although statistically significant, may not be clinically meaningful. There are little to no data on the outcomes of these tests.

Lastly, ASCP believes that it is important for physicians and patients to use the DTC test results as a mechanism to discuss a variety of health-related issues and future laboratory testing needs, if necessary.

It is essential for patients who choose to engage in DTC testing to select a CLIA-certified laboratory and to have their test results reviewed by their primary care physician.

On behalf of ASCP, I commend FDA for addressing this important issue and thank FDA for giving me a chance to

speak.

(Applause.)

MS. SERRANO: Okay. And actually our last speaker of this session is going to be Gaia Bernstein.

MS. BERNSTEIN: Good afternoon. My name is Gaia Bernstein. I'm a Law Professor at Seton Hall University School of Law and a member of the Gibbons Institute of Law, Science and Technology and the Health Law and Pharmaceutical Law Center built for the Seton Hall University School of Law.

I have written extensively about law and genetics. And much of my research is advocated through removal of barriers to genetic testing. I have written a lot about the need to alleviate fears of genetic discrimination in order to encourage genetic testing.

But with the direct to consumer genetic testing, I feel that we have to start thinking about regulating the flow of genetic information and to think about what genetic information is actually beneficial.

And I believe that individuals can't make these decisions without a medical professional guiding them. The medical professional, in my view, is vital as a gatekeeper to genetic information.

Now, currently, the dominant paradigm is diagnostic paradigm. For adult onset disease an individual goes to a physician and tests usually for a specific disease that may be prevalent in his family or he wants to confirm a diagnosis and he consults with a physician or genetic counselor, before undergoing the testing and receives the results from the person.

Now, with direct to consumer genetic testing, we are seeing a new paradigm. We are seeing a consumer paradigm. This testing is usually sold over the Internet. They are sold in packages. Usually you test from something between 25 to over 100 conditions, depending on the company, and the individual does not see, in most cases, a physician or a genetic counselor when making the choice to test.

In addition, the tests are marketed in a less serious manner. They are marketed in order to satisfy curiosity as a social endeavor. You might receive the test as a Christmas gift from Aunt Betty.

Now, so without a lot of consideration, an individual can undergo a large panel of tests and receive all these results alone when accessing a website by himself.

I do not believe we should have these two separate paradigms. I think even when a company sells a battery

of genetic tests, there should be a medical professional consulting the individual, both at the beginning of the process when deciding what test to undertake and when receiving the results.

Now, some states currently have laws which require that medical professionals will prescribe the tests and some genetic testing, direct to consumer genetic testing companies have a physician on staff describing the tests. I do not think this is a satisfactory solution.

Now, the policy debate is mainly centered about latter stage of interpreting the results. But I'm concerned also about initial stage of selecting what test to undertake.

Now, I believe that it is important to have medical professionals at this beginning stage for two reasons. First of all, because some information may not be suitable. People may not want to know. Some people may not want to know certain genetic information about themselves.

For example, some people may not want to know that they are going to get Alzheimer's later on in life. Now, if there is a medical professional involved and the tests are not bundled together, then the medical professional can explain to the individual what the diseases are, whether there are any preventive measures and then the individual can make an informed choice of

whether she wants to test for all these conditions and what information she can cope with.

The second reason why I believe there is a need for a medical professional at the beginning stage is that not all genetic information is that useful. And if an individual tests for many, many conditions, this causes the problem of interpretation at the latter stage. Because if you get many positive results, the abundance of results might obscure the important data.

So basically to conclude, I haven't spoken much about the interpretation stage, but the previous speakers have spoken about the complexity of interpreting the results, and I believe there has to be a medical professional who will represent the individual who will not be a representative for the company, because there is an inherent conflict between the interest of an individual at the beginning of deciding what test to take and the representative of the company who will prefer the individual, in most cases, to purchase as many tests as possible.

To conclude, I think the law should require a medical professional to represent the individual who is not a representative of the company. Thank you very much.

(Applause.)

DR. GUTIERREZ: That concludes the public

speakers for that session. Thank you very much. I would like to proceed to have the commentators, invite the commentators, to join me at the table and we will proceed with the next session.

Moderating this session is going to be Muin Khoury, he is from the CDC, and will be introducing the commentators and moderating the session.

DR. KHOURY: Good afternoon. So this is going to be a very interesting session, so I'm waiting for my speakers to show up here. Just by the way of background, I'm the Director of the Centers for Disease Control and Prevention Office of Public Health Genomics.

And our office has been created with the purpose of figuring out how to use genomic advances to improve health and prevent disease at the population level.

So among other things, we have been recently paying a lot of attention to the issue of direct to consumer genomic tests. We have been examining their scientific foundation as many of the previous speakers talked about.

We have also been conducting public health surveillance to figure out the extent of our wellness use and practices among consumers and health care providers and figuring out what the public health response should be.

So the topic of this session is about DTCs for LDTs and it looks like although there are non-genomic tests that could be used in a direct to consumer fashion, it looks like the whole discussion has been primarily driven by genomics.

So I don't want to completely close the discussion to genomics and genetics, so the panelists feel free to use other examples as well.

By now, you have already heard about the various issues that the LDT community faces, whether it is DTC or not DTC. So I think our particular panel this afternoon will have to explore to what extent the issues of DTCs are different from non-DTCs with respect to LDTs. I mean, just too many alphabet soup here, but you guys know what I'm talking about.

So we have a great lineup. I would like to introduce our panelists. Sue Friedman from the FORCE, Facing Our Risk for Cancer Empowered, a consumer-based organization. She is the founder. It's a support group for patients and families affected by hereditary cancer or cancer risk.

Susanne Haga, a scholar from the Duke Institute of Genomic Sciences and Policy.

Ann Willey, who is well-known from the New York Department of Health, Office of Lab Policy and Planning, at the

New York State Department of Health. And she has been threatening to retire for a while and I hope she doesn't.

We have also Wayne Rosenkrans, President and Chairman of the Personalized Medicine Coalition.

And Vance Vanier, CEO and President of Navigenics, one of the companies that is offering DTC genetic testing services.

So welcome to all. And I would like to explore the issues at hand. Let me first read to you the big sort of the framing questions that you all have and based on what you heard this afternoon and your own thoughts, I would like to pick your brain on a few of these things.

So the first issue is to consider what are the major concerns of DTC testing in general? And are they different in scope? That some of the issues that we have been hearing over the last two days and with respect to lab-developed tests.

In other words, are the issues with respect to offering a genome profile on-line or through services, should they be treated differently or exceptionally than what the LDT community has been facing?

And in particular, I would like to explore both the benefits and harms or potential benefits and harms as well as the

cost of these things.

So given that direct to consumer issues potentially could lead to misinformation or are there any concerns about consumer fraud or things of that sort?

So I want to start and I would like to first hear each one of your perspectives on the overarching question, are LDT DTCs different from LDT non-DTCs? In other words, are we in a different framework of thinking than the past day and a half worth of discussions?

So maybe we will start with Ann?

DR. WILLEY: I think Dr. Sulkes attempted to make the distinction between direct to consumer in the drug markets, which is marketing and education as to the availability of the product and then the referral of the interested consumer to the health care delivery system for accessing that product through prescription for that drug.

There is a model within the FDA for medical devices which also allows direct to consumer access to tests through the over-the-counter lab test device approval process. Those devices have generally been devices which are simple.

You take them home and you do them yourself, like the home pregnancy test or home cholesterol test or a home

glucometer test. And you either have interacted with a health care provider in the past who has recommended your use of this device or they are really allowed for direct to consumer access.

When we move into direct access testing of tests performed in a laboratory, and I think we are talking mostly CLIA-approved licensed appropriate laboratories, but the marketing is often being done by an intermediary, not the laboratory that is going to do the test, perhaps an entity that is going to interpret the data, sometimes an entity that is not really doing either, they are just going to take your money and arrange to send the specimen.

We are really talking about a different kind of testing. And if these assays like most genetic tests are lab-developed tests, they are not going to fit in the model that the FDA has used in the past, a simple reliable well-established self-directed test.

So I do think direct to consumer marketing of LDTs are fraught with different issues than the traditional over-the-counter patient access to an assay that they can perform themselves.

DR. KHOURY: Any thoughts?

DR. VANIER: You know, I would say a core set of

issues that we have heard through the last two days are certainly shared by genetic testing and those ways are similar to all LDTs, i.e., issues of analytic validity and clinical validity. And just as there are thousands of tests currently that may have had less than a stringent regulatory framework, obviously, new emerging tests, you know, still fall within that realm.

I think, however, as I listened to the testimony of the last eight speakers or so, what I believe is different in this case is the angst and the sets of issues that revolve around the actual delivery of this information.

And in this case, I think it is extremely important to understand when you look at the genetic testing industry in general, there is no uniform genetic testing industry, just as there is a wide range of pharmaceutical companies that have different codes of behavior and different approaches to the market. And there is a huge range of physicians that range in their understanding and their areas of expertise, so, too, is there a wide range of philosophies and approaches within, you know, be it consumer genomics or personal genomics or whatever you want to call it.

And I think it is instructive to look at kind of both ends of the spectrum, right? So in general, we have on one side

of the spectrum, you know, call them genomic libertarians, you know, they believe that consumers should have unfettered access to their genetic information without any kind of, you know, mandate of health care support.

And on the other end of the spectrum, you have, obviously, heard testimony today that points to a belief that it's really physicians and only physicians that should be empowered to order this sort of testing and interpret it on behalf of their patients.

And I think as we have clearly heard in the last two days, the pros and cons of each side of the spectrum, I think, are getting increasingly well-understood, right? It's on the genomic libertarian side. You know, most of those advocates would say that this is information that the public has a high level of interest for.

It's information that can be harnessed to motivate lifestyle and behavior change, which is sorely needed by our society, given the epidemic of preventable disease out there. And in some ways, I think, this is an evolution of an ongoing theme.

We have seen at least for the last decade of the sort of next generation of consumer empowerment, is what these

advocates would state. So, you know, you have the Institute of Medicine's 2001 report that stated that they believe the health care system should be re-engineered to enable consumer empowerment.

And obviously, everyone in the room knows that study after study shows that when consumers get more engaged, they have better outcomes in their health.

Obviously, the appropriate concerns expressed today and the cons of this side of the spectrum are a belief and concern that the information might cause misuse and lead to emotional harm, which is usually the rationale for the other end of the spectrum we have heard today, which is it's really the physician that is in the best position to order the test and act on the information on behalf of their patient.

And I think that makes absolutely a certain level of sense. However, there are critics out there that would challenge the physician as the appropriate gatekeeper for this information. As we all know, there is a huge genetic education lack right now in the physician community.

Hundreds of thousands of physicians certainly do not have genetics as their medical -- in their medical school curriculum. And furthermore, we know that it takes on average

20 years for physicians to adopt new technologies.

And so the question remains and the concern is that if you make the physician the gatekeeper, will you stifle innovation and patient benefit, etcetera, etcetera?

And just to finish my remarks on this, I think a lot of what we are hearing here is part of an overall societal reexamination of the physician and patient relationship.

You know, it seems hard to imagine that it was no fewer than 30 years ago where oncologists would hide diagnoses from their patients. It seems hard to believe that 15 years ago there is concern whether patients should have access to their own HIV testing.

And, you know, certainly, I think all of us in the room look back on this through the lens of modernity and see that these are issues that come from a bygone era. And certainly everyone in the room today can get access to their own HIV test and their own paternity test, all of which are profoundly impactful emotional information.

And the open question, I think, for industry and for regulatory bodies like this is is genetic information any more risky than what we already allow out in the public today?

And, you know, putting all the rhetoric aside, I

believe that for complex issues like this, the right answer is somewhere in the middle in sort of a thoughtful moderate approach that at least for direct to consumer or direct access testing for genetics, you know, we really are in the early years of an industry.

We absolutely need educational support and genetics is at its best when it is partnered with programs and services that can help patients affect the information that they learn.

And so for our company specifically, this is why we only address the market through physicians and in wellness programs. But I think there is room for a broader and more inclusive paradigm where it is not simply physicians that can serve as gatekeepers, but genetic counselors and pharmacists that should be able to play a role in this in the future.

DR. KHOURY: Go ahead.

DR. ROSENKRANS: I want to always resist the urge to say ditto at points like this. You know, I believe --

DR. VANIER: You can.

DR. ROSENKRANS: -- the answer to the basic question is, you know, is there a difference between sort of first generation LDT tests that have gone to DTC and the glucometers,

etcetera, and, you know, the next generation that we are seeing now and the future generations, once we have the $1,000 genome available and can look at whole genome scans rather than 20 SNP arrays?

The answer is a definitively yes. We heard several times within the last series of presentations that we really are dealing with a new paradigm here. And I think that's true.

The underlying business models that we see within this area are still emerging. We have new companies forming. We have new ways of dealing with the various issues that are put forward and it's all somewhat experimental at this point.

So I think we have sort of an interesting dilemma in front of us. How do we act responsibly to protect the public, if they need protected, yet not squash the needed innovation in this field as it moves forward?

And that is always a difficult tightrope to walk, but I think we are going to have to proceed very carefully, very cautiously as we think about what meaningful regulation is in this area, how it should be applied and how we move forward.

I think there are clear pros and cons and we have heard both sides very avidly, both yesterday and today on this

issue. I think there is a clear need for standards and most of the participants in this new industry agree for that. The question is who does the standards?

There are a number of organizations that I think can be looked to provide that third-party standardization. That again is characteristic of an emerging area of a new paradigm that is forming.

You know, I think this whole question that really bothers a lot of the academics and I was in industry, I was in the pharmaceutical industry and now I'm an academic, about, you know, is this nothing more than genomics for estate planning?

And I think the answer is we don't know yet, but it probably is a lot more than that. But we have to give it time to really form and come about. The whole question of interpretation, standardization of the test. Once we have standardization, how are the tests interpreted?

We heard some very eloquent talks in the last several minutes about that issue, but then the question becomes who does the interpretation? I mean the sad fact is, and Vance just mentioned this, you get outside of the major academic centers on the east and west coast, Cleveland Clinic, etcetera, most physicians don't know how to interpret a genetic test.

Most of them haven't even had a genetics course since they were in high school or an undergrad in college. So I think the expectation that the physician is the only potential moderator/interpreter of these data is probably not going to be able to work.

So we have to think about what are meaningful alternatives? Genetic counseling? Not available everywhere readily. I'm thinking in my wife's hometown, a very small farming town in South Central Iowa, the nearest facility that does any kind of genetic interpretation is in Des Moines or in Sioux City, six, seven, eight hours away from her hometown.

And the hometown physician, the primary care physician for all the people in that town is, at this point, 85 years-old. He is the only game in town. He doesn't have a clue what genetic information is. And that's most of the country. It's not those of us that are located in the major medical centers.

So a lot of work to be done. We have to proceed carefully. We have to proceed with great study and we need to collect data, because we don't have much right now. And we need to create incentives to produce that data and ways of capturing and interpreting that data as we move this new industry in this new paradigm forward.

DR. KHOURY: Susanne?

DR. HAGA: Coming from an academic medical center on the east coast, I would concur with the previous speaker that many of our physicians and physicians outside of the academic medical centers don't have a lot of genetics training, mostly because they were educated many, many years ago prior to this genetics and genomics movement.

And, secondly, because it's not relevant to their clinical practice, so it hasn't been a mainstay of their continuing education practices. It was a very, very small part of their formal medical education.

And so I have to wonder whether physician-ordered LDTs are any better or worse than consumer-ordered LDTs if we are looking at the issue of delivery of genetic tests or of LDTs. And so when Muin was asking about differences between DTC LDTs versus standard physician-ordered LDTs, it is the delivery of the information and that's, I think, what many of the risks are focused on.

But if you look at the tests and FDA's role of the tests and oversight of the tests, I think regardless of who is ordering the tests that the same criteria should apply, that the tests should be analytically valid, the tests should have clinical

validity and some type of clinical utility.

But clinical utility is a very ambiguous term and when you bring in consumers and why they are ordering these tests for various purposes, clinical utility is broadened with personal utility and personal curiosity and you are adopted and you don't have a family history. There is a whole host of reasons why consumers may be seeking these services outside of the physician.

They may have skepticism about federal legislation and the protections against discrimination and so forth and so choose to order these tests and so forth.

But I think for today's discussion, if we separate some of the issues that are related specifically to delivery of the tests, which FDA may or may not have jurisdiction or oversight of, from the actual test itself and the concerns that we have heard about clinical validity and analytical validity, we can define which stakeholder groups have an opportunity to reduce the risks that have been raised concerning DTC tests and be able to ameliorate the risk and so forth without saying it's all in one group or another.

DR. KHOURY: Sue?

DR. FRIEDMAN: So, a lot of my experience, actually all my experience, in this topic has less to do with the

different types of tests, but it does have to do with the marketing of the tests.

And I think it is very difficult to separate direct to consumer testing from direct to consumer marketing, because how are consumers learning about the test, unless there has been some marketing of it?

And where we have seen the impact and where we have seen it affect consumers is in the delivery of the information, and what is being told to consumers, what is being told to their health care providers about these tests and the knowledge that people are making real-life decisions based on that information.

And so our experience comes in a field where there really hasn't been much oversight as far as I can tell, as far as we can tell with regard to the messaging that the companies are delivering to consumers and also to health care providers.

And, you know, I agree it is challenging, because physicians can order tests, but what we are seeing a lot of is, unfortunately, that they are ordering the wrong tests, they are misinterpreting it and, you know, I mean, we have case examples and, you know, at what point do they stop being anecdotal and start being, this is a trend in people making health care decisions

based on incomplete information, incorrect information, biased information.

And unfortunately, it is being facilitated by health care providers who just don't have the training in genetics. So the area that I see as a big need is -- and, you know, I don't know if that would fall under the FDA jurisdiction, but, oversight on the claims, on how the companies are marketing it, how they are educating doctors, whether or not they are allowed to and able to provide continuing education credit for doctors and provide unbiased and asymmetric information.

And, you know, I mean, we do have cases where women have acted on it, having surgery based on an incorrect test being ordered and then finding out that, you know, they were told they had a BRCA mutation and they didn't, they had a variant.

You know, I mean, I think a good first step is that the FDA has started to accept, through MedWatch, some of the reports from health care professionals about adverse events. And I think it is really difficult to know how consumers are acting on this and, you know, what the body count may be if we are not starting to measure where these cases are.

DR. KHOURY: Okay. Thank you all for this first pass here. So let's dig a bit deeper into this. So we have heard

from you and from the previous speakers that this is all emerging, it's all experimental and we need to collect more data.

We have even heard from 23andMe that this is a new way of doing research, sort of mixing research with practice.

Now, we have also heard concerns about the need for informed consent and confidentiality. When you start doing research on an area, that this is sort of a bit different than selling a product, that people assume that there is some value behind it.

So in this emerging era where our genome -- which I agree if you want to have access to your genome, you can have access to your genome, no one is going to stop you from that, although most of the information will be either useless right now or insufficient to act upon.

So what do you all think about this new model, the emergence of mixing research and practice? Is there any danger from doing that in a free market economy where consumers may be confused by what they are buying? I mean, they are learning something every day. They are maybe changing. Today you might be told you are at increased risk of Type II Diabetes. Tomorrow you might be told, no, no, no, we changed our mind, you are at decreased risk of Type II Diabetes.

And actually, this is based on a scientific paper that I reviewed recently. So this emerging information that is still in the research mode, consumers are paying for it. And they may or may not have the protection. So what would you say to that?

You don't all have to answer that question. People who want to jump in and have their voice heard, let me know.

DR. FRIEDMAN: I guess I'll say and speak to the point about, this is where it is so important to have health care experts who have expertise in the area of whatever the test is, so that they can have an ongoing relationship with the patient and the patient can understand what it means when new information emerges and what it will mean for their health.

DR. KHOURY: So, Sue, just to pick on you, so are you concerned, as a consumer, that people may make life-changing decisions on the basis of information which if it changes tomorrow, it's too late?

DR. FRIEDMAN: Well, I mean, that can happen anyway. And, you know, we know of a case where, I believe, a BRCA mutation that was a variant that was suspected deleterious was changed to suspected not to be deleterious and so that can happen in any realm.

So I don't know inherently if the fact that it is DTC changes it, although at least in the case of people who have had genetic counseling, they were able to be reached through their genetic counselor and, you know, so there is a continuity of care there that I think is important.

DR. KHOURY: Ann?

DR. WILLEY: Well, you have all heard several times about the unique New York State model. So, we could either say our answer is simpler or our answer is more difficult.

But that we would clearly segregate participation in research from access to approved laboratory tests or clinical decision making. Those labs that offer lab tests for clinical decision making that are lab-developed have submitted those assays and they been reviewed and they have been approved, whether it's a genetic test, a chemical test, toxicology test.

So the labs that are offering direct to consumer information to tell them to go to a physician to have the test ordered, because New York state is not a direct access test state, you must have a physician's order to access clinical labs.

So the physician has ordered the test. New York State also has unique consent requirements, specifically for genetic tests and for genetics research. So, if the patient agrees

to have a clinical genetic test, that lab can do that test and no other test. They can ask permission of the patient to keep the specimen for research purposes, but it has to be de-identified.

So, if the lab were to create a new test in the future, submit it and have it approved, they could notify the physician who originally ordered the test that a new test is available.

Now, in genome profiling we have made a unique exception. The genome profiles there in the database of the approved laboratory, they were only authorized to report those markers which have proven analytical and clinical validity.

They now have a marker that they think has new analytical and clinical validity. They won't have to test the patient again, but they will have to get an order from the physician in order to go back into the data, analyze the data and now report the new test for clinical decision making.

So we've separated research which gets done without reporting back to the patient. And clinically valid reported decision making tools that get reported when a physician requests that new information. Complicated? Yes.

DR. KHOURY: So, Ann, just before you answer, do you think the information in the genome profiles are clinically

valid from the New York Department of Health?

DR. WILLEY: For those few markers that the labs have been approved to report. Navigenics can only report a certain set of their markers. Another laboratory that has a permit in genetic testing can only report those assays that they have submitted, have been reviewed, and based on the literature there is apparent clinical validity.

DR. VANIER: I think, first of all, I can attest that New York's quality process is extremely stringent and Dr. Willey definitely knows what she's talking about. But it does speak to an assertion that I would like to push back on, which I think it feels to me that there is an assumption here that there is little evidence and little data around tests like these.

And I think it's important to actually review what is the state of the literature base, because it is by no means absent. And if you look at the literature base between clinical validity, you know, the quality of the genetic marker and then clinical utility, what are the behavior outcomes of using this information, both from a safety and efficacy standpoint?

And, certainly, if we look at the validity, you know, as Dr. Khoury and his own group published a set of criteria called the Venice Criteria from the CDC, which designates what is a high

quality GWA study, what are markers that one can begin to understand from a standardized framework are of high clinical validity value.

And, certainly, for our approach, that is the particular framework that we use and in cases exceed when we're selecting markers that go on the panel.

So I think there are particular arenas and specifically focused markers where there is good association data that we can begin to think of it from a clinical validity standpoint. And, certainly, our New York process was an excellent training exercise for that.

From a clinical behavior and utility standpoint, you know, we've heard a lot of fear today about misuse of information. But I think it's important to point out that we have a decent body of literature that comes out of the rare monogenic testing area and comes from conditions that, you know, one would theorize are much more frightening than then the more preventable conditions that we look at today.

Huntington's disease being the poster child example. And, you know, for example if you look at that literature, if you test for Huntington's disease, if you test for breast cancer, if you test for long QT, et cetera, et cetera, in no cases

have those studies showed any long-term psychological consequences.

The reverse is true as well that there is an emerging body of data. It is absolutely still small and limited, but growing, which shows that people feel empowered when they get this information. There's early data that shows that when you are -- if you believe you are an increased genetic risk for obesity, you'll start dieting.

If you are at increased risk for Alzheimer's, as you all know from the REVEAL Study last year, you are one year later and more likely to be medically compliant with diet and exercise, et cetera.

And so I think by no means would anyone say that the work is done. Indeed, something that will be quite exciting is Dr. Eric Topol, who is a PI on a trial coming out of Scripps Translational Institute in California, just submitted a study in which he will show that thousands of people who took this sort of testing showed no sort of anxiety or untoward effects.

Clearly, I think an issue going on there is there is self-selection bias. People who choose to do this kind of testing are information seekers who are probably psychologically resilient in seeking this kind of information. But I think, obviously, society

is a long, long way off evidentiarially speaking where this should become mandated testing by any stretch of the imagination. But there is absolutely early safety and efficacy data there.

DR. ROSENKRANS: I think, actually, the question that Muin is posing is a bit broader than just in this context. And it really gets to really what is the nature of clinical research in the Facebook/Twitter world? It's definitely different from what it has been.

And we are just beginning to grapple with what that means. You know, patient reported outcomes, the various patient advocacy databases that are starting to be used by drug companies to look for anecdotal evidence of new indications, et cetera. This is a whole new world that we really haven't dealt with and it needs to be looked at in terms of, you know, I hate to say it, but the tyranny of the RCT.

You know, what does that -- what happens to the RCT trial in light of massive data sets that might be accumulating outside of the normal controls. And there's lots of pieces here that need to be thought of and again I go back to, let's not throw the baby out with the bath water.

We just don't know how to use all of this yet, but we will. And we need to make sure it's there for us to use

effectively.

DR. HAGA: Just to your point about the new wave of recruiting research participants, I think the key issue or the crux of it is making sure participants/ consumers understand what they are signing up for.

So they are signing up, they may be coming to the site to purchase a test and then they are also asked if they want to participate in the research. I think making those two very, very distinct, I don't know what you call it, approaches is clear as can be or is critical. It's not obvious to me that someone checking off a box has really read the informed consent form and understands what it means, because we all check off things and sign things that we don't read and I don't think this is anything different.

But the problem with research, we find this in standard clinical trials that someone signs up, we sit down with them, we explain what's in the informed consent form and actually read paragraphs to them and six months later they come back and it's for their follow-up or something and they are not -- they have no recollection that they actually signed up for a research study.

And that suggests that they really didn't understand what they were signing up for in the beginning or they were signing up for different reasons and got confused and so

forth.

So I think that's the crux to the issue. And I think it's also related to a lot of problems is making sure that the consumer/ potential research participant understands what they are actually signing up for. And so maybe if they do check, "yes, I would like to participate," that a follow-up call would help clarify to both the company and to the potential perspective research participant that they are also signing up to participate and what that means and what that entails for them.

DR. FRIEDMAN: I just want to add something, too. I mean, I am all in favor of research and I think it is potentially an exciting way to propel research into, you know, the next era. And I don't know that it necessarily has to be, do we restrict this type of research versus do we start measuring it and seeing what the outcome is?

Do we find out? Do people understand what they are consenting to? Maybe somewhere between absolute restriction and, you know, unfettered access, we can start putting those regulations in place and start measuring it. And, you know, see if people do understand what they're signing up for.

DR. KHOURY: Okay. Thank you. I would like people to start lining up if they have questions while I pose my last

question to the panel here.

I think you mentioned the Venice criteria and a couple of years ago the NIH and CDC held a workshop that many of you participated at on the Scientific Foundation for Person Genomics.

So we are quite familiar with the outcome of that workshop. And in that workshop, you know, we discussed sort of how the field is evolving and how that information is needed at any given point in time.

But, you know, what concerns me, and I am not an unbiased observer here, because I have been observing the field for a while, is that if you -- many people who have sought these services today and there has been publications on this, one of them in Nature last October by Craig Venter where five or six or seven people had their results by four different companies.

And for the same diseases, one said it's up, one said it's down, and the other said, you know, it's not increased or decreased. So, you know, one or more of these companies are wrong. And it's on the basis of the same platforms, the same scientific literature, so one of the things we talked about in that workshop is that for industry-wide standards to come up with interpretation of the literature. And I think the PMC was

beginning to do some of that.

And I am wondering, what is the status of industry policing itself in that field, rather than relying on FDA or CLIA or some other groups to do it for them.

DR. ROSENKRANS: Yes, indeed, I remember that meeting. And, you know, there was -- there is an avid desire on the part of the current industry participants for standardization. They recognize it now. This is not good for patients. Moreover, it's not good for business. And something needs to be done.

In fact, there was a letter that went from 23andMe to Francis Collins at NIH and to Peggy Hamburg at FDA asking for standards. The question is who's going to do it? And, you know, it's probably a conflict of interest to expect the companies themselves to do it. And, you know, even if they were to offer to do it they may not be believed, having been in the pharma industry for 30 years, I can tell you, you know, how that works.

So there needs -- there is a crying need for standards organizations to take this up.

We have a couple of candidates for that. There is NIST, it could move into the biological area and take over on something like this. There is the United States Diagnostic

Standards Organization, that has just been founded to do exactly this kind of work. So, as happens often in a new and emerging paradigm like this, the need for standards emerges quickly.

And the organizations to handle the standards emerge with it. So I think the status right now is that there is -- you know, throughout the industry recognition that standards are essential. And we are starting to see the tool kit emerge that could actually enable the setting of these standards through an objective third-party.

DR. KHOURY: Let's take some questions.

DR. HUDSON: Kathy Hudson from the NIH. We heard at the beginning of this meeting that FDA is intending to put together a risk-based strategy for regulating LDTs. And my question to the panel is how should they look at direct to consumer testing?

Should it be a characteristic that increases the risk of the test and is built into the initial stratification or should it be considered as a second order characteristic of whether or not tests that are high risk should be offered DTC or not?

You know, I heard a lot of interesting observations about DTC, but I didn't really hear how you are advising the FDA to consider DTC in their new oversight system.

DR. KHOURY: Ann?

DR. WILLEY: To date, the FDA's approach to direct to consumer if we equate that to direct access, this is available only for the simplest, best-characterized appropriate self-use test. That included home HIV testing in an appropriate context of preimposed test counseling or a home pregnancy test.

In New York State, the only tests that are available for direct access testing by a client are those tests which have been approved by the FDA for over-the-counter access. That would be only the simplest, least risk, lowest risk, best qualified tests. So I would hope that the FDA would consider any kind of high risk test as not appropriate for direct access testing.

It doesn't mean you can't continue to market it as something that's available, but it's available through appropriate medical access routes.

DR. VANIER: I think the challenge -- I believe Dr. Becker showed a graph that showed a stepwise plateau of risk. And I look at it as a physician, as well as a consumer and it makes intuitive sense to me how that graph was constructed. But I think many of us would be hard-pressed to actually put written standardized guidelines around what defines risk.

Because I think one running theme that you've

heard in the last two hours is when an extraordinarily personal experience it is when each person understands the risk. And certain things that a physician may assume a patient may be interested in risk, it may not be the case. He may be interested in other information. And so, you know, I suspect from our own standpoint we may be similar to some of the other LDT insights you're hearing here, which is, you know, regulate on the quality of the science, regulate on the quality of the clinical validity. And that will be an extremely important first step as you begin to address some of the breadth of issues that are happening in DTC market.

DR. ROSENKRANS: Yes, I agree. The regulation must be based on the science. I am always a little nervous when I hear about sort of staged areas of risk. Class I, class II, class III, somebody has to create the criteria for those. And that can be hell on wheels to do as you put those together.

So I am a little nervous about how well that will work, but it keeps coming back to the basic science. How good is the science? And how informed is it? How well accepted is it? What is the evidence base? It starts to stratify things a little bit, perhaps better than sort of ephemeral criteria.

The question about marketing practices, this is an

interesting one. Now, there is actually some precedence within FDA, its part of the FDA organization, it's called DDMAC, which actually sets regulations around marketing for pharmaceutical products in the DTC world.

And there has been a lot of work done over there on how to look at marketing practices, so there may be some learnings that can be garnered from that in terms of controlling this state.

But I think, just going back to agree, it needs to go back to the science the quality of the science, the quality of the data and the evidence base. I wouldn't wrap artificial characterization around it.

DR. HAGA: I concur and it's what I said earlier that I think, whether it's DTC or not it's the test that is the issue and that FDA should oversee an LDT anyway it's offered. Looking at it in validity and clinical validity with that said, however, I think there are other opportunities for different groups to step in and address some of the concerns that many of us have expressed about the implication of the test results on consumers.

The need for drastically more educational resources, perhaps some type of comparison shopping guide. I mean, there is more information on which HDTV to buy, than

which genomic testing service to purchase from. The jargon and everything when you buy something, a new product, is confusing to all consumers, regardless if it's genetics or it's a home appliance or whatever.

And I think there is a great need for both public health organizations, laboratories, professional medical organizations, NIH or CDC, you name it, to step up and provide greater educational resources to inform patients or, excuse me, consumers about these products. But that the test itself should still have the same review parameters as any test, DTC or otherwise.

DR. KHOURY: You should all have been on the education panel which is coming up in 15 minutes. So anything to add?

DR. FRIEDMAN: Yes. I think we need to look beyond the quality of science. Like you said, we need to look at the test and how it's going to be used. There are some good science behind BRCA testing and some of the DTC or Direct Access testing does include BRCA tests within the panels. And so, you know, personally, I'm in favor of the New York State model and hope that the FDA will look at that.

DR. KHOURY: Another question?

AUDIENCE MEMBER: There's been a lot of discussion about comparing DTC testing as compared to traditional clinical testing. But what I haven't really heard much discussion about is, in terms of difference between the two, the basic business or rather evolving business model of direct to consumer, it appears to me that originally DTC was meant to generate income by offering a service to a customer.

The customer purchases the service. And the information is then provided to the customer. That model doesn't seem to have been particularly successful in terms of generating a lot of income for this industry. And what I've seen the industry move towards are avenues of generating income beyond directly providing the service to a customer.

But using that information derived from the customer and in many ways, many ways which are not necessarily specifically communicated to the customer, some companies are starting to move in the right direction. For example, I know there has been a lot of attention to 23andMe's -- 23andWe's, rather -- consent provision requiring specific consent for participating in studies that are going to be published in peer reviewed journals.

But those same consent forms, for example, by 23andWe state that if it's not going to be published in a peer

reviewed journal, it can be used for other purposes without consent from the consumer.

And I think there are other companies that are using the original consent as a blanket, you know, blanket ability to use that information however they see. So I would like to hear a little bit more discussion about the business model of direct to consumer. And how they intend on perpetuating that business model as they develop and grow.

DR. KHOURY: Any thoughts?

DR. VANIER: I think again I would remind the audience there is no one business model in this industry. There are a myriad of many. And are there business models that are predicated on reselling the information in some way to other parties? Absolutely.

Are there business models as personally -- are there business models that I do not agree with, for instance, that include using the genetic information and implying that you can then sell people vitamins or foods to fix their genome? Unfortunately, yes.

Our own model, because I can't speak for ourselves, still absolutely relies on providing the test results to the customer and that's it.

We think, in the early years of this industry, privacy and data security are absolutely paramount, not only legally but by perception, and that trust is extraordinarily important or you can go down a very slippery slope, where patients, consumers and physicians can doubt your motivations. And certainly we can see certain examples of that in every industry of health care, pharmaceutical industry as well.

So if the core of the question is are there different business models? Absolutely. If the core of the question is how can we regulate these business models? I think that's much more of a difficult question and probably revolves around the transparency of the consent process, be it for research or be it for use of the data.

DR. WILLEY: And I won't bore you with another several hours, but New York State also regulates the business practices of the laboratories that it approves. And so some of these models about how the money flows and who can have access to the information are specified in New York State statute and reg.

DR. KHOURY: Any other questions from the audience? Yes.

MR. LAM: My name is Tony Lam and I represent

myself. I have had 25 or more years of IVD experience working at the FDA, but now getting into the LDT space. From these two days of hearing all the presenters and the panel talking about not wanting FDA to be in the LDT business and also unavoidable collateral damage, I would say that we all know that, you know, how we get into this LDT, DTC mess is the weakness or non-existence of the CLIA Regulations.

So if you want to do something, we should suggest that form a government and LDT Task Force to fix the problem. But FDA has a wealth of information about safety and effectiveness and experience, so invite FDA to be a partner to fix it.

So that would avoid, you know, a lot of problems and would level the playing field. The second point is that -- use third- party reviewers so you completely, but not FDA reviewers, so that way you get the benefit of not having -- draining FDA resources and at the same time, who knows, you might spur a new industry and save the industry, save the economy.

At the same time, the third point is that I'm always a proponent of the equality systems and to repair the or improve the quality system of CLIA Regulations. We should model after the QSR, because QSR is based on ISO9000, and it could be applied to any business like toys or toothbrush or medical

device. So that way everybody would be happy. Right?

DR. KHOURY: Was that a question somewhere or was that a closing statement? All right.

MR. LAM: Was a comment.

DR. KHOURY: Comment. Thank you for the comment. Any comment on the comment or we can close the session? I want to thank all of you for being here today and we can move on to the next session. Thank you.

(Applause.)

DR. GUTIERREZ: So we're going to go ahead and move on, so we can finish as soon as we can. The next session, actually, I think I believe there is only two -- three commentators, so we'll start with that.

MS. SERRANO: So our first speaker of the session is going to be Mya Thomae.

MS. THOMAE: Good afternoon. I'm Mya Thomae. I am CEO of a small regulatory consulting company. And normally when I do regulatory presentations in the afternoon, I find it's helpful to bring a little chocolate, as we tend to all glaze over with all of this information. Unfortunately, I wasn't able to do that today.

So I'm going to be commenting on what things I

think would be helpful in education and outreach.

We have been working with a number of the LDT companies ever since IVDMIA to get them in compliance with FDA Compliance Regulations.

So, as we have heard today, CLIA and QSR are not matching standards. Existing clinical labs may be missing one or more of the following systems: Design control, supplier control, process validation, complaints, adverse events, medical device reporting and clinical testing.

A key education and outreach question is how best to help existing labs succeed under the new enforcement standards. Absent a final IVDMIA Rule, many companies were unsure which standard might apply. We've advised many of our clients to develop to the IVD standard, in particular design control. Many current LDT products are already well on their way to IVD compliance or actually in compliance with FDA Regulations right now.

Lessons learned can inform other labs and the FDA as to industry best practices for compliance. So with this change, many labs will face quite a bit of work around development, quality systems and clinical testing work. This change will be unwelcome to many, but it is not the end of the

world. Trust me, we have gone through it with a couple of clients already. And, in fact, it can be a good thing.

Much of this work is aimed at proving clinical utility, and that is an important selling point for any diagnostic, whether or not it's required under our regulatory framework. FDA should emphasize the shared interest in clinical utility so that the new paradigm is not framed as a pointless exercise in paperwork.

The one thing I stress to all my clients is, leave enough time. And enforcement changes this big may take years to fully implement. Even so there is very little time to waste. Development and clinical testing can take many years to complete. In particular, start planning now for sample -- clinical sample acquisition. And, please, don't make the assumption that retrospective samples will be sufficient.

In some cases we have been able to make that work, but in other cases we simply have not. FDA should also clearly communicate timelines, but keep the pressure on. So far delay has equaled confusion for many of our clients.

Clinical testing will be a high hurdle, but is not your first order of business. Prior to beginning clinical work, ensure quality systems are under control. In particular, make

sure your assays are under change control. If assays are changing throughout a clinical trial, it can be very difficult to show that the data you've collected is valid for the final test that you want to market.

One area that's not on my slides, but I have been thinking about a lot during the last two days is also if FDA could help us understand how software will need to be validated in that LDT paradigm, that would be very helpful.

There are guidance documents on over-the-counter software, but given that the labs will not have access necessarily to a lot of the background information on how software is developed, giving us some guidance on how to do that will be very helpful.

Also, I will stress again, any help you can give us with design control and how to apply it for laboratory-developed tests will be appreciated. So labs do need to become sophisticated with the new paradigm and FDA can help via education and outreach.

FDA should also clarify and adjust policy to provide labs the maximum opportunity to survive this transition.

So this one's a little small, sorry about that, but a couple of things I would like to like to just put out there. A grace

period on an initial submission would be very helpful. In the neighborhood of two years, I think, would be about right to get people up to speed. That seems to be the period of time that folks are able to come into compliance in.

With design control, if you could give us a little extra time after that, that would be very helpful. And this is what we did when QSR was initially implemented a number of years ago.

Finally, if you could give us some mock inspections -- I know the compliance folks are always really busy -- but if you could come in, do some mock inspections, I think that might be very helpful, both for the FDA inspectors or the CLIA inspectors, whoever ends up doing this, as well as industry.

So I implore you, grace, but not delay. Please, please, keep this moving but as much structure as you can give us would be helpful.

Clarifying inspection procedures and looking ahead. The sky is not falling. And some products may not survive this transition. But I also believe that many won't become possible until this is complete. And establishing a higher baseline of quality and accuracy will be good for the diagnostic industry in the long run and even for most individual labs. Thank

you very much.

(Applause.)

MS. SERRANO: Our second presenter is Ashley Gould.

MS. GOULD: Thank you. I just wanted to point out with all the discussion about the need for physician intermediary and sort of the discussion of fear that was on the previous panel, that we have been involved with two ongoing studies, one with Stanford and one with Johns Hopkins University.

And the data will be published soon for those. And I think it would be really useful to see that people seem to really be understanding the data that they are collecting through services like ours.

So more broadly in terms of education, there has been a lot of discussion about what FDA will be doing to help LDTs. And I'm going to focus a little bit more on how individuals can use genetic information and whose responsibility it is to ensure physicians can use this information.

So three years ago there were fewer than 100 Genome-Wide Association Studies and today there are over 2,000, with new studies published each week. Making this information useful to physicians is critical for personalized care and we believe

education is an important first step to moving towards integration into clinical care.

23andMe believes education and greater understanding of genetics across the population both for individuals and physicians alike is critical. And part of our mission is to be involved in this effort.

As was discussed earlier, we have animated four educational videos that are available on our public website. And there have been over 140,000 views on YouTube of our Genetics 101 video. We think this is a great contribution and an example of the ability to promote widespread education in a digestible format.

We also believe that a personal genome service itself is another important educational tool, as learning in the context of your own genetics is powerful. We provide context including describing and citing published literature that reports are based on providing average population risk, noting the contribution of environmental factors, providing next steps like talking with your doctor or genetic counselor. We've also implemented the ability for customers to talk with genetic counselors through an independent company.

Our blog is another important educational tool.

As new research is published and important discussions take place in the industry, we blog about them and provide timely discussion on these topics in an easy-to-read format.

We have a very active and engaged customer community where customers also discuss topics with each other and engage with 23andMe.

We think it's important that physicians can explore their own genetic data to think about integration into clinical practice. We've offered free genotyping to hundreds of physicians as a result. We've received important feedback and will continue to seek out additional feedback.

We're also getting involved in medical school programs. There has been a lot of discussion earlier about the need for physicians to understand genetics better. And we think it's important to start at the medical school level to talk about genetics and clinical care impact.

We also hosted a policy forum last week together with California State Senator Alex Padilla, gathering together MDs, genetic counselors, academics, bioethicists, individuals from industry, media and science, to discuss important social, technical, ethical and policy issues.

And I think it's important to note that one of the

key findings from the day was that everybody agreed more empirical data is needed to assess what the risks, if any, of the kind of testing that we're providing are.

We believe we have a powerful opportunity to positively impact public health while providing individuals access to their genetic information.

Colleen McBride at NIH has been involved in a number of research projects studying access to this information and has published that individuals who present to health care providers with online genetics information may be among the most motivated to take steps toward healthier lifestyles. These motives might be leveraged by health care providers to promote positive health outcomes.

So we believe that in order for genetic information to become a routine part of medical care, it will take the participation of individuals, industry, government and the medical community. Physicians will need point of care tools developed to access as the genetic information grows, both directly to the consumer and in the medical office.

And this is happening at a rapid pace. We believe the education and outreach we are undertaking is a critical first step to the integration of genetic information and

information of other laboratory tests will be well-integrated into clinical care in a comprehensive and meaningful way. And we look forward to continuing discussions with the FDA on these important topics. Thank you.

(Applause.)

MS. SERRANO: Okay. And our last speaker is Balaji Srinivasan. He'll have to give you his last name. I'm just going to do a quick switch here.

DR. SRINIVASAN: Hi, everybody. My name is Balaji Srinivasan. I'm the CTO of a genomics startup. But I also teach computational genomics and statistics at Stanford. And I would like to speak here today in my capacity as an academic and as an educator.

I have three very specific proposals for areas of education that I think would be very helpful. I'll post slides later, but these three areas are basically for patients, physicians and labs.

So for patients, you know, what we want to know about is how can we balance the coming ubiquity of personal genomes sequences with the reality that 60% of people don't know that tomatoes have DNA.

Okay, it's a fact, you can see the polls. With

respect to physicians, how do we empower medical professionals at large to, you know, give patients information about genome sequences while also acknowledging the fact that there are highly trained sub-specialties in medical genetics and pathology that do understand genetics and have been interpreting it for many years.

And then third, with respect to clinical labs, how do we translate an existing LDT into an IVD submission? And how do we provide an analytically valid genome sequence that can be, you know, then the basis for subsequent determinations?

Regarding educating patients about their genome, there is a precedent for this. So one question is, how do we educate people to be good stewards of their car? Okay, you know, how do we ensure that people know the rules of the road? How do we acknowledge the ubiquity of automobiles while balancing that with the importance and the risks? And how do we basically ensure that people don't hurt themselves and others while operating an automobile?

And what we do is we have a driver's license exam. You establish by an exam that you are not a risk to yourself and to others. And, you know, that's not just true for driver's licenses, but pilot's licenses, board certifications, bar certifications, you name it. There's all kinds of things where a

license to operate is given by an exam with the appropriate training.

And genomics is actually no exception. There is a very important precedent -- if we're talking about education well, Harvard is the name, and recently Harvard's PGP, actually, the Personal Genome Project, issued an entrance exam to ensure that all participants had genetic literacy.

So by this exam they covered all kinds of things, including the fact that one is potentially disclosing family history, that one is getting information about potentially incurable diseases, that one's children may be at risk for conditions and, you know, also the limitations of genetic information and the fact that it's no panacea.

And this entrance exam has proven quite a success. And similar to a driver's license, it ensures that people know the limitation of genetics. It acknowledges the coming ubiquity of personal genomics and balances that with the importance and the risks.

And, basically, it's a way to ensure that people don't hurt themselves and others a way that is accepted in many other very high-stakes areas of societies like flying planes and driving cars where death can result if there is an error.

So that is proposal number one, to follow Harvard's precedent and start thinking about what an appropriate educational program would look like for someone to be an informed operator of their own genome, just like we are operators of our own computers and cars and planes.

So proposal two regards physicians. How do we educate physicians about the genome? There's actually a mechanism for doing this for updating positions on new information, it's called CME, Continuing Medical Education. You know, how many people here have heard of CME?

Okay. So if you're talking about, you know, transmitting information and empowering physicians, we shouldn't just say, you know, MDs don't know genetics. We should do something about that. There should be standardized CME modules where after you pass them, you then have, maybe not the equivalent of a full sub-specialty in medical genetics, but certainly enough understanding that one can prescribe pharmacogenomics or carrier testing or what have you.

And use this established process to bring MDs up to speed on genetics. That's proposal number two.

And finally, the third proposal is really, you know, a couple of things in one. But basically, how can labs adapt to the

coming IVD Regulation? How can we provide an analytically valid genome sequence? And what I think would be perhaps the single most useful thing that could be done would be a web forum for 510(k) submission with several full, approved examples of things that the Agency thinks are good.

And how many people here think that that would be handy? Okay. So that's something that is currently not available on the web, but there are teams that are doing this at data.gov at other initiatives. People are out there that can actually computerize things that are currently paper records and that can bring that kind of technology to the Agency. And the Agency probably has the capabilities themselves.

So those would be the three proposals. Number one to follow Harvard's precedent and start thinking about ways to empower people to use their own genome.

Number two to have physicians updated on genomics via CME.

And number three to actually have worked examples in a web forum for 510(k) submission, so that everyone can see what is necessary. Thank you.

(Applause.)

DR. GUTIERREZ: Thank you. We're going to

proceed then with our last group of commentators. And for this Joan Scott from the Genetics Public Policy Center is going to be our moderator.

I actually would like to ask to thank Ashley Gould for pointing out that the FDA isn't infallible and that without telling us up front that we missed the s in Johns Hopkins and I understand that's quite an insult, so I would like to apologize to Joan for actually putting that on paper, Johns Hopkins.

MS. SCOTT: Well it just speaks to my own spelling ability that I didn't even notice it, so thank you all.

Well, first of all, thank you to the FDA for inviting all of us to be here. And I want to thank the audience for staying here to the very bitter end, it has been a long but, I think, very informative and useful two days.

So the purpose of this last panel is to talk about the education and outreach efforts that will be needed within the laboratory and the wider community as FDA goes down this path for increasing oversight of laboratory-developed tests.

And we have certainly heard from a number of speakers today that the world that the clinical laboratory and the language that the current laboratory world speaks is not necessarily the same as the FDA language. And so how can we

bridge that?

So today on our panel are a number of individuals who have spent quite a bit of time thinking about these issues related to laboratory-developed tests. We have Dr. William Castellani, who is the Medical Director of Clinical Chemistry and Professor of Pathology at Penn State Hershey Medical Center and he's also Regional Commissioner and Inspection Inspector for the College of American Pathologists Laboratory Accreditation Program. And he's the CAP liaison to the International Organization of Standardization Technical Committee.

We also have, next to Dr. Castellani is Ms. Sharon Terry who is the President and CEO of Genetic Alliance. Next to Sharon, we have Dr. Kathy Hudson who is Chief of Staff at the National Institutes of Health. And lastly, we have Dr. Elisabeth Kato who is the staff service fellow at the Center for Outcomes and Evidence Agency for Healthcare Research or ARC.

So I am going to start with a couple of questions that the FDA had specifically wanted us to address during this panel session. But I'm also going to open it up to the panel to also jump in and ask questions and perhaps we can engage in a dialogue and help get down to some of the -- pick away at some of the nuances here. And then we'll open it up for comments

from the floor.

So, first of all, just about sort of this educational gap around between what laboratories are used to dealing and the language that they are used to dealing with through the CLIA and moving into sort of a more FDA role. What are the needs going to be for the laboratories and how do we meet them? What resources are already potentially available?

Dr. Castellani, do you want to start with that?

DR. CASTELLANI: Sure. I think that the biggest experience that we have had as getting involved in as a dean status accreditor for CLIA is, basically, we need to have regulatory clarity. We need to understand what is expected of the laboratory. And, therefore, we can educate as part of the accreditation process.

For example, in the evolution of the CAP ASCP Guidelines for testing as they were developed which the nice thing about it was we were involved in developing the guidelines. We also then undertook an educational process for our accredited laboratories and held them to compliance at the point when they became familiar with what the testing really needed to have done to be properly executed for patient care.

In this way, we can serve as an accrediting agency

and also as an educator. I think that is really where the interface between the regulations and the laboratory currently exist. And the accreditors that go into the laboratory have the opportunity to be to -- as much evaluate the laboratory as well as to help educate the laboratory.

DR. HUDSON: I thought Gail Vance put it very well in her comments about how laboratories currently have little to no interaction with FDA and don't speak FDA-ese. And so I think being able to generate people who are bilingual, speak both languages, the CLIA laboratory and FDA language is going to be important.

What role, who has the responsibility of really helping to inform the laboratories about what these requirements really mean for them, I think is an interesting question. The CAP and other voluntary and professional societies certainly could play a big role.

I think we also have an opportunity now with the agencies working, the federal health agencies, together in an unprecedented way. Peggy Hamburg and Francis Collins working together on the Vision for Personalized Medicine and on a whole host of issues together with the FDA, NIH Leadership Council.

We are now reaching out to the new head of CMS

to talk about ways in which we could work together. And so I think the agencies working together could probably be helpful in sort of pulling their resources and expertise and making this transition period as less painful as possible.

MS. SCOTT: So I'm going to come back to that in a minute, Kathy, but I want to unpack the issue of what the labs need a little more, because it seems to me there are all different levels of and experiences of labs.

So who is most at risk for being left behind or most in need? In the idea of leaving no lab behind. If we want to make that our new motto.

DR. CASTELLANI: Well, I would say that the laboratories that are represented in this audience are not the ones who are going to be left behind. They are the ones who are familiar with regulation, have an ability, have a group of people that will review the regulations and help implement them in whatever language they are written.

It's the smaller laboratories that serve their own patient population. The laboratories that really are out there trying to -- concerned and focused on what their clinicians need and do what they need to do to provide those services, if at all possible, that will need the help, that will need the support,

whether it be through professional societies, through accreditors and through actual training programs for laboratory directories as well as for other laboratorians.

Those are the laboratories that we will need in our most risk for not being able to comply for lack of understanding. And if I may make a separate comment, one of the issues that the FDA will have is because of the fact that to the laboratories the FDA exists as this nebulous entity. There is no direct interaction with the FDA. And actually to some extent there was no drug integration with CMS when CLIA was first promoted.

The problem becomes there are a lot of laboratories out there. And there becomes -- if there is an informational vacuum, there will be people who will fill that vacuum. And, they will interpret the guidelines, not necessarily -- and you will wonder where did this come from? I was part of the lab -- I have been part of the Laboratory Accreditation Program and I've been a reviewing commissioner for eighteen years.

Early on as a Deputy Commissioner, I attended a forum at ASEC and the presenter, who was not a pathologist, was not a laboratory director, was not a member of the CAP, started to interpret the CAP Guidelines, the checklist requirements.

And I was thinking to myself either he doesn't know them or I don't know them. There is a problem here.

And I was early on in my tenure as a reviewing commissioner that I wanted to make sure that I wasn't wrong, because I had just, in fact, reviewed a laboratory, removed a deficiency which is based on exactly what the commentator was commenting on.

And the reality was, I was not wrong. And that's what these laboratories will have to deal with. There will be conflicting information out there. And without the clarity and the interpretation and the interface, and I don't think FDA can do it, it has to be another group. The labs will go wrong, not because they don't intend upon following the requirements, it's because they never really were trained or understood them to begin with.

MS. SCOTT: Thank you. Sharon?

MS. TERRY: I think going forward if FDA enforces oversight over LDTs then perhaps something like they are doing with the orphan products division which is a kind of, you know, show that goes on the road to help in that case, small companies develop orphan drugs and to unpack how do you do an orphan drug submission, might be applicable here in the same kind of system where labs were educated directly by the FDA,

since as Gail said there is no parlance between them at this point.

MS. SCOTT: Do you want to say an additional word about the rare disease community?

MS. TERRY: Sure. So I think there is a sense that if there is a great deal of oversight and its onerous, then, of course, the rare disease tests won't live up to the specifications.

I think a couple things. I think, one, we haven't heard very much today and we definitely should make sure that it is understood that there is a federal program administered by the NIH through the Office of the Director called the CET program. Which stands for Collaboration, Education and Test translation and that is a program in which a small lab, usually, a disease organization and a clinician come forward with an idea for a test and they are given $1,000 per EXON to develop that test.

The disease group is given $1,000 for educational materials about the test. And together the three entities put together a test for the disease. It has been extremely successful. The data is then deposited in the de-identified manner into dbGaP and connected to other Federal Databases.

Right now I understand that that program, and Kathy could probably say more about this, has been funded by the Office of Rare Disease Research. And there is some question

about the availability of funding going forward and the Office of the Director is looking at that.

MS. SCOTT: So what are other resources available currently? We have heard about CAP, obviously, runs a lot of educational programs, but there are other resources available. And we do have individuals from other agencies here so maybe they can speak to some of those resources.

DR. KATO: I would like to speak a little bit about some of the resources that ARHQ could bring to the table. We are mostly concerned with somewhat more downstream situations. What really is the impact of a test on patient outcomes?

Going beyond the analytical validity and the clinical validity to try to establish is there clinical utility? And ARHQ has three, I think, different areas of expertise that could be brought into the process.

First of all, we have a network of evidence-based practice centers, which synthesize existing evidence about new medical interventions and might be helpful as a way of centralizing the very studies that go on concerning different medical tests and then making them available to professional societies and interested labs to find out really what is the state of evidence

about a particular test.

We also do technical briefs, which are fairly quick summaries of what information is known about new and emerging medical intervention or, in this case, tests which really focuses on what are the key questions or what is the research that needs to be done, so that we can use this intervention with confidence?

Again, that might help to generate the kind of evidence that we've heard there is such a need for. ARHQ also can help to generate directly some of the information that's needed to underpin these tests as they go forward.

And finally, ARHQ has started to offer continuing education. In fact, for both systematic reviews of existing evidence on medical interventions and also for methodology of evaluating evidence. At the moment, we really only have modules for medical education and pharmacy education, but there is no reason that we couldn't extend to laboratory tests as well.

MS. SCOTT: One of the things that have been brought up a couple of times over the last couple of days is the Genetic Test Registry that NIH is proposing. Kathy, can you speak a few words about that and how that may fill some of the information gaps?

DR. HUDSON: Sure. So the NIH's role here is predominately in supporting research and also in supporting resources that are useful both to scientists, clinicians and to the public. The National Center for Biotechnology Information at the National Library of Medicine has a wealth of resources including PubMed, PubMed Central, OMIM, Genetics Home Resource, a whole ton of resources related to the genome.

And when Dr. Collins became the head of the NIH, he decided to go ahead and put in place and follow-up on the recommendations of the Secretary's Advisory Committee on Genetics Health and Society, which was to create a Genetic Testing Registry.

So we have the informatics expertise. We have the clinical genetics expertise. And so we thought we might as well just go ahead and just do it. So we now have requested comment from you and other stakeholders about what would be important to include in this registry.

What would be burdensome? What would be beneficial to different groups of stakeholders? And we are hoping to have a registry up and running early next year.

We have requests out for comments that's open until August 2nd, and once we have those comments in hand, and

have an opportunity to review them, we will be announcing a public meeting. And in our public meeting I hope that I don't have to have the stamina that you guys have had sitting here all day long listening attentively.

MS. SCOTT: It has also been brought up rather extensively, particularly in the last session, around the need for education outreach to the wider community, beyond just the laboratory community who is going to be most immediately and directly affected by whatever changes, but more broadly.

An education, you know, I think we can all get on board with saying education is a good thing. What specifically would you recommend FDA's role be in education or outreach or communication with a broader community beyond the immediate clinical lab?

MS. TERRY: So I think FDA's role is primarily to be core source material. And I see an ecosystem growing up around that that includes professional societies, includes laboratories themselves, includes certainly consumer groups, disease groups, NIH when it does it's activities as well.

I think there is a role for the kind of engagement that this is. For example, I am pleased that this is much more engaging than four years ago when the IVDMIA Guidance hearing

was held. This has felt more interactive.

It would probably be nice if you guys could say something back occasionally. That would be real interesting. I would recommend that.

(Applause.)

MS. TERRY: And then I think there is a role for more integrated activity between the agencies, because again, you know, this is a regulatory Agency. There are other agencies that are meant to do education, certainly CDC and others.

And the other piece I wonder is if the, you know, many times over the last two days, it has been said that this is difficult material, particularly for the public or for the consumer. And the label is the place FDA educates or contributes to information. And then again, I think the ecosystem around the label and the understanding of the clinicians who use the test, as well as, I absolutely believe, consumers are becoming more and more savvy about consuming or participating in their own health care.

So I think part of the overall health literacy has to include something about why and how tests are approved and who approves them and why they get approved.

DR. CASTELLANI: I agree. And I think that

there has to be a lot of education or information directed by the FDA to clinicians and to patients. And, in part, also to understand what are the limits of FDA- approval? It is not that the FDA is going to guarantee a test. And sometimes the public does not really understand that.

The FDA has a certain role in evaluating a test and in ensuring that claims are justified and that they have merit.

But we all -- I have been in the lab too long to know that methods are not fool proof. They cannot be. The need to be followed-up. Whether they are in vitro diagnostics or whether they are laboratory- developed tests, they need to be followed-up.

And one of the issues becomes, for the FDA, are you putting yourselves as guarantors of the quality of the test? And to some extent, that's the public perception. And I wonder if you really want to be that, that guaranteeing agency?

DR. KATO: Just to add I think it's perhaps related to labeling, but helping consumers and also, you know, physicians who are not necessarily in academic centers to understand what the approval means and what it doesn't mean. What the tests can show and what the tests can't show. I think is a very important direction.

DR. HUDSON: I think FDA's willingness now to enter into the LDT marketplace is really important, in part because of this strange issue with the label. So we have had a number of drugs something like 10% now of drugs have some sort of genetic information in the label.

And that sometimes just says that a gene is involved in the metabolism of the drug, duh, or that a specific variant influences the metabolism of a drug in a specific way, and that physicians should have that testing performed. But in no case, that I am aware of, does the label say this specific FDA-cleared test is the test that is matched to this drug.

And so by entering into the LDT space, I think we are going to be able to expect more from what the label tells both the physician and the patient about what test is available, which test is a good test, and then how do I use that in order to make decisions with my patient?

DR. CASTELLANI: The issue of the label is, to me, also very important. It's what CLIA requires in terms of informing the user, the end user of the results. And as a member of or as an expert on ISO TC 212 thank, God, we are group one not work group three. For those of you who understand, work group three spent years on European labeling.

I am not going to talk about and it's not FDA-labeling, it is the European Union labeling process. And what we have at least from the FDA-labeling requirements is something that is more meaningful to the user and can be communicated through to the clinician by the laboratory director when it's necessary and I think that's a very important role.

MS. SCOTT: If there are individuals who have questions that want to come up while I ask my last one, please do.

So we heard in yesterday's presentation, I think it was by Dr. Mansfield, about different mechanisms that FDA has with communicating with outside groups like, guidance documents, IVD forums, PreIDE programs, informational meetings, advisory panels, direct questions to FDA I think we are all on her list, I was taking dutiful notes.

Of all of those mechanisms are there others that they should employ or think about as particularly as this transition period starts to unfold about as movement starts getting made?

DR. HUDSON: The one thing I would add is, and this was mentioned, FDA does a very good job about making information about what they do public. It's sometimes a little hard to find, but it's there. And I think that especially as people start to get used to whatever it is that FDA decides to do, that

people are going to be watching others. And so to the extent that that process is very transparent and that the information about the first guys through the process is available, everybody else is going to be watching that and to the extent that that's easily available, will be important.

DR. CASTELLANI: I believe that the process needs to engage the stakeholders and also go through a structured rule making approach which has been mentioned in the past by other people that, in fact, that is a good mechanism for both, explaining the intent and the desire of the FDA and also to get feedback as to where the pitfalls might happen to be and where other areas of concern or possible misunderstanding might be in the area of being regulated.

DR. HUDSON: So you used the word rule making there and I am wondering if you're using it sort of with real precision that you are supporting when FDA moves forward, that they go through formal notice and comment rule making or if you are sort of using it more generically and that the guidance process that the FDA has proposed is adequate, in your view?

DR. CASTELLANI: I believe that the stance of the college has been a formalized rule making process.

DR. HUDSON: And just to follow-up, so is there

anything that the formal notice and proposed rule making process enables FDA or forces FDA to do that they couldn't do through guidance process?

DR. CASTELLANI: It allows an organized process of explaining ideas and then responding to the comments that are then received.

DR. HUDSON: Requires it, yes.

DR. CASTELLANI: Right.

DR. HUDSON: Okay. Thank you.

MS. SCOTT: You would find that helpful from your perspective to have that clarity and that precision?

DR. CASTELLANI: When we first looked at the CLIA requirements, the rule making process helped us to understand really where CMS was coming from. And I think that was very important in understanding and developing our own educational tools and our own accreditation requirements.

MS. SCOTT: Here first and then here.

MR. O'LEARY: Thank you. I also share my great admiration for the endurance of the FDA officials here for two days. Good job. I would just like to provide some macro advice as having been a marketer for a couple of decades.

I think the FDA and fellow agencies and HHS

initially kind of do themselves a great disservice by virtue of how language gets used. And words matter, language is very important and beltway legalese is an important language here, but the rest of the country does not understand it and it puts distance between you and your constituents that are regulated in ways that are unnecessary.

And I would encourage you to think very carefully about how you use language. So to be honest, most people don't know the difference between a clearance and an approval.

They mean a lot to you and I know they mean a lot in law, but to the world they get mixed up all the time, because they are too close to each other and it wasn't thought through how to word these things in a way that people could understand.

So we have 510(k)s which makes it sound like you are a division of the IRS. And we have other -- you know, there is PMAs. There are Google PMAs. There are 8,000 societies that call themselves some kind of PMA thing. So there are lots of better ways to communicate that wouldn't be that hard. And as Sharon pointed out a minute ago, you guys are sort of a source document for a lot of the rest of HSS.

You have a lot of power. If you took control of the language and tried to make it more user-friendly, I think that

other parts of HSS would buy into that. You could have common language, you wouldn't have people calling genetic tests that have no DNA involvement, that kind of thing, which is a problem now and I think it would significantly help overall regulation, but especially this effort you're undertaking which will go well beyond the laboratorians that you are communicating with initially.

Health care providers beyond physicians, including nurses and pharmacists, will get involved in this and, ultimately, many patients especially those with chronic disease who will be needing these tests potentially over years, will also become very cognizant. They will also be consumers, if you will, of FDA language.

And so I would encourage you guys to take the opportunity to revisit how you use language, try to enforce it across HSS with your sister agencies to the extent that that is feasible. And make sure that there isn't 18 different language sets coming out of Washington that are all legalese that nobody else understands.

So I know you get what I am saying, I am sure you have heard it before, but I think it's a great easy win for FDA as you go forward into this next stage.

MS. SCOTT: Thank you for that comment.

Anyone want to add anything to that? Go. Good language. Over here.

MR. O'LEARY: Dan O'Leary, Ombu Enterprises. This is going to be more in the nature of a comment than a question, but I would be interested in the panels' reaction. So in medical device manufacturing, which is basically my background, there is an extensive set of regulations, registrations, listening and so on. But I am going to address myself primarily to the quality system part.

So what I have learned particularly with Panel 2 is that laboratories are really good at running tests. They are not really good at understanding test manufacture. And I am not to say that they make bad of LDTs. What I am saying is they don't understand things like design control, supplier management, all of that sort of stuff, because that's basically not the business they are in.

If they were to buy a test from a kit manufacturer, that kit manufacturer would understand all of those things. I think what I am learning is that the FDA is going to say laboratories that develop tests are manufacturers and you are going to have to follow the device regulations.

And one of the things you're going to end up

having to follow is QSR. So I would argue that you cannot effectively integrate QSR into CLIA in the sense that they serve two very different functions. One is how to run tests and produce test results. The other is how to manufacture and develop tests. Now there are linkages, but I am hoping that what will happen in the end if the FDA heads this way, that they will actually use QSR because we understand QSR.

There's thousands of people that are out there that understand it, that can explain it, that know how it works, rather than breaking up some new manufacturing paradigm in regulatory language that gets introduced for the first time.

And I will give you -- introducing QSR was a good exercise for FDA. The other thing that happened was that hospitals suddenly became manufacturers when they got involved in single use, reworking single use devices.

All right. The FDA classified them as manufacturers. They had to implement QSR. They went through all the growing pains that you're going through now. The FDA did a wonderful job, as I understand it. I wasn't directly involved in helping the hospitals make the transition to their new role. So I think it's possible, we have got some good examples and I think it will be successful. But I don't think it will move all

that quickly. Thank you.

MS. SCOTT: Any comments on the comment? Go ahead.

DR. CASTELLANI: I think that there is an interface and I think what needs to be looked at is how to coordinate with what is in CLIA, with CMS to bridge the gap between again the manufacturing role that the FDA may see for laboratory-developed tests, as well as the performing role that CMS considers for the rest of the testing and, actually, all of the testing that's done.

There was an attempt and I think that to some extent it's actually fairly good and the ISO 5189 document to look at to sort of adapt the 9001 quality system to a medical laboratory doesn't -- it's not exactly a very good fit. But it can be done.

And I think that that's something that may need to be investigated. And I wouldn't say necessarily used as a complete model, but at least give some sense to CMS what can be done.

DR. WILBER: I'm Judy Wilber from Independent Consultant and also Clinical Laboratory Director at XDx.

In the spirit of all the talk of bilingual and education, I would like to respectfully suggest that the FDA also

learn clinical laboratory-ese, so that -- and I mean by that to actually go on CAP inspections and get a handle on what the clinical laboratory is.

You know, there is a lot of talk of, you know, trying to turn the laboratory into a manufacturer, but also just to see exactly what it is that's done in order to validate tests within the clinical laboratory. And then how new regulations might fit that.

MS. BORGES: Hi. Katherine Borges, International Society of Genetic Genealogy. This was actually part of my speech before I got the hook, so I thought since the panel brought up this subject and also the last portion, the last session was on consumer education, I just wanted to comment on it, because it has only been touched upon briefly here.

I have heard it mentioned one or two times, but I feel that you should bring in as far as the DTC tests go, bring in the FTC, because the FTC is -- their role is for consumer education. And they are wonderful at developing literature and educating the consumers and when there is fraudulent, you know, processes going on.

And then another Federal Agency to bring in, too, would be NIST to set standards. You know, a lot of people here

today have talked about, you know, how do you determine risk and all these other things with the complexities of DNA. But that's what NIST does is they set standards.

And finally, FDA's regulatory requirements on DTC's could be met with something as simple as full and adequate disclosures. You know, there is so many products out there already that have warning labels on them like cigarettes, alcohol.

You mentioned that test earlier the one that a gene test does have a disclosure on it, so I just wanted to bring that up that involvement by other Federal Agencies would be very helpful. Thank you.

DR. CASTELLANI: If I may go back to the prior commenter just to mention that there is there a role for FDA to understand what the accreditors can actually do for evaluating laboratory-developed tests and for ensuring proper compliance.

Because the issue can be -- it's huge. If you think about it, the CAP Laboratory Accreditation Program accredits 6,700 laboratories. The majority of these -- a small number of these laboratories are limited service laboratories or black labs that are really all moderate complexity or even wave testing, so that's not a problem.

But there is a large percentage, the majority, that

are high complexity laboratories, that each one of them has, I won't say one, but probably multiple laboratory-developed tests. And if you look at -- if you consider the region that I oversee the inter-region that is -- that has a high concentration, if not completely made up, of Academic Medical Centers and esoteric reference laboratories.

It's a lot of fun to review those laboratories. It helps me really understand the cutting edge of laboratory medicine and I think its, personal aside, the best volunteer position of the entire college.

But that means that there is a -- I have over 110 inspections. And some of these just in the inter-region. And some of these inspections include not only sections, but actually free-standing or separate laboratories that are totally developed, that are totally dedicated to laboratory-developed tests. That's their entire test menu.

And by whatever risk classification, a high percentage of these esoteric tests are going to fall into at least a moderate, if not a high risk category.

There is a large -- there's going to be a very large demand placed on the FDA for this purpose.

And just to talk about the college, consider that

the laboratories that we are involved with, they are the ones that are writing the papers. They are the ones that are doing the peer review. They are the ones that are providing the resource committee members. They are our inspectors.

And there are other accreditors out there that are peer-based and they can provide a resource.

MS. SCOTT: Thank you. We have one last question.

DR. VLADUTIU: Yes. I had a question, but I also wanted to make a comment. I have never been to a meeting like this and I wanted to say I have heard people talk here and met people here that I would never meet in any other venue of the scientific meetings I attend. So thank you for that. I mean, it was just an amazing experience.

I'm Georgirene Vladutiu, SUNY Buffalo. I wanted to ask, I think it's so incredibly important to educate physicians about genetic testing. We have a wealth of resources with the National Association of Genetic Counselors and I know the president was here. Is there any way that something can come out of this meeting toward that first module as one speaker said or a symposium for physicians bringing together many of the people that spoke here, but not for five minute talks with a hook and just

try to educate them with CME or course?

I mean that's the only way you are going to get them. I think genetic testing cannot succeed without the education of physicians who are going to have to be that interface. And I wish genetic counselors could be encouraged. I mean they want to be involved. I wish they could be put into positions where they are involved more and more.

MS. TERRY: So I would recommend you put an abstract in for the NSGC Conference in the fall, that would be one thing. I certainly think quite seriously that the professional societies do have the opportunity to educate. I'm a member of the American Society of Human Genetics and certainly that meeting always has conversations like this happening there.

And then there are special symposium throughout the year. Genetic Alliance, in fact, ran about three years ago, Eyes on the Prize, true telling about genetic testing with a lot of the same people who are on panels. So I think I would encourage you to encourage that, whether it's national or local. And certainly use the consumer societies the National Coalition of Health Professional Education and Genetics is another organization that could help with this sort of thing.

DR. VLADUTIU: I think there should be a

regulatory component, too though, with the FDA.

MS. TERRY: Right. And for example, at our meeting we did have CDC, FDA, CMS, all represented.

MS. SCOTT: So just to close if you could just give a last comment about what you think the next step should for FDA should be mainly around the issue of education and outreach. But if you want to, you know, talk more broadly you can do that too.

DR. KATO: Well, probably a few more sessions like this to further flush out, you know, what some of the concerns are and who needs to be involved. I think also maybe reaching out to some of the FDA sister agencies to explore what kinds of resources are available throughout HHS to bring to bear on the question of educating everyone who needs to be involved, the laboratorians, but then also patients and clinicians.

DR. HUDSON: I think the next step is for FDA to draft the draft guidance and get it out there for people to react to. I think we've been sort of waiting for a number of years for something to happen and now we're on the precipice, so I think the next most important thing is for FDA to get a draft out for us all to be able to react to and comment on and then move from there.

MS. TERRY: What she said.

DR. CASTELLANI: Well, from my personal viewpoint, I think what the FDA -- where the FDA should go is to define the question and then look for those stakeholders and resources that are out there to help flush out the answers.

We've talked here in this session about what the laboratory does in terms of modifying tests, we talked about in this session about genetic testing, we've talked about direct to consumer testing. That's a heterogenous group of tests and being offered by a heterogenous group of laboratories to a heterogenous population.

The FDA, I think, may very well be served by identifying where the major concerns happen to be, and then working with the stakeholders to flush out the best way to go forward in an incremental way.

MS. SCOTT: Thank you everyone.

(Applause.)

DR. GUTIERREZ: So I'm going to take a few minutes just to close the meeting. I actually want to begin perhaps by, you know, saying that yes, it was a little difficult sitting up there for two days, but this was the idea of my boss, so I made him sit with me, which you can appreciate that.

And, yes, you know, there are times that we

wanted to, obviously, answer either criticism or questions. I was a little, you know, taken back with the idea that we need to perhaps better self- regulate ourselves and think about language that we create and we put in the stratospheres, so perhaps IVDMIA is not the most easily understood concept and we need to think about how to communicate a little bit better.

But what I really wanted to do was to thank the moderators. I think they did a wonderful job the four moderators really kept things going very, very nicely and the commentators. We really got a lot of good discussion and, obviously, thank all the participants. All of you that came and provided a five minute discussion or the questions you asked.

This has really been a very good meeting for us. This has been very rich and we will get a lot out of this. And I would like to thank Jeff for standing up here, for sitting there and for introducing the meeting incident here for two days and Dr. Sharfstein for actually making the time to come and really portray what an important issue this is for us and the FDA and how willingly we want to move forward in this.

And last but not least, I would like to thank a lot of people who really put a lot of time in preparing this meeting and making things happen. A lot of work went behind the scenes and

particularly I would like to thank Courtney, Liz, and Katie, because they really did a wonderful job.

(Applause.)

DR. GUTIERREZ: And lastly, I just want to say, you know, my predecessor, Steve Gutman, used to leave all the talks, but towards the end of his career with the FDA, he left it with some poems to ponder on, but he used to before that always leave with the idea that this is all about good science as he spoke to that before.

And it really is about really good science and putting good science in terms of what is best for public health. What makes sense? How do we regulate it that makes sense? And in the end it's really all about the patients. And I would like you to keep that in mind as we move forward. Thank you.

(Applause.)

(Whereupon, the meeting was concluded at 4:54 p.m.)